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ACTION OF DIGITALIS IN COMPENSATED HEART DISEASE

HAROLD J. STEWART, M.D.

NORMAN F. CRANE, M.D.

JOHN E. DEITRICK, M.D.

AND

W. P. THOMPSON, M.D.

NEW YORK

A report [1] has already been made concerning certain effects on the circulation caused by the giving of therapeutic amounts of digitalis to normal persons and to patients suffering from organic heart disease who exhibit signs and symptoms of congestive heart failure. In the case of the normal heart, the action of digitalis was to decrease its size and the volume of its output of blood per minute; [1] in the case of the enlarged heart, whether the rhythm was regular or that of auricular fibrillation, the action was to decrease its size and to increase its output of blood per minute.[2] There was one action of digitalis which was common to the normal and to the enlarged heart, namely, the effect on size, which was to decrease it. We were led, then, to the notion that this action was an essential one and that the cardiac output which resulted depended on the initial size of the heart. Moreover, the effect on the size of the heart appeared to be due to an action of the drug on the cardiac muscle, since we were unable to show that the decrease in the size of the heart and the decrease in cardiac output which we observed were associated with a decrease in venous pressure.[1] Moreover, results parallel to these were found when observations were made on normal

From the New York Hospital and the Department of Medicine, Cornell University Medical College.

An abstract of these studies was presented before the American Society for Clinical Investigation, Atlantic City, N. J., May 6, 1935.

1. Stewart, H. J., and Cohn, A. E.: III. Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart, J. Clin. Investigation **11**:917 (Sept.) 1932.

2. (*a*) Stewart, H. J.; Deitrick, J. E.; Crane, N. F., and Wheeler, C. H.: Action of Digitalis in Uncompensated Heart Disease, Arch. Int. Med., this issue, p. 569. (*b*) Stewart and Cohn.[1]

dogs,[3] as well as on dogs with large hearts without failure.[4] The results so far as cardiac output was concerned were similar to those reported by Burwell, Neighbors and Regen [5] (for normal human beings) and by Harrison and Leonard [6] (for normal dogs).

In continuing the study of the action of digitalis we observed the effect of giving the drug to patients suffering from organic heart disease who had not experienced congestive heart failure. Studies were made not alone of patients with a regular rhythm but also of those exhibiting auricular fibrillation. There was reason, as a matter of fact, for observing the action of digitalis in those patients exhibiting normal rhythm, since Christian [7] has advocated its use in these cases.

I. OBSERVATIONS ON PATIENTS EXHIBITING NORMAL SINUS RHYTHM

We wished to reduce our observations to as standardized a procedure as possible in order to compare the results obtained in different patients. To this end we chose, in the first place, for this part of the study only those subjects who satisfied the following criteria: (*a*) All the patients exhibited signs of organic valvular disease of rheumatic origin; (*b*) patients were chosen who had not suffered from an attack of congestive heart failure or who did not have heart failure at the time of observation; (*c*) the patients had heart disease either of type I (activity not limited) or of type IIA (activity slightly limited), as described in the publication entitled "Criteria for the Classification and Diagnosis of Heart Disease" issued by the Heart Committee of the New York Tuberculosis and Health Association; [8] (*d*) patients were given within twenty-four hours the same amount of digitalis, namely 1.6 to 1.8 Gm. of the same "batch." [9]

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3. Cohn, A. E., and Stewart, H. J.: The Relation Between Cardiac Size and Cardiac Output per Minute Following the Administration of Digitalis in Normal Dogs, J. Clin. Investigation **6**:53 (Aug.) 1928.

4. Cohn, A. E., and Stewart, H. J.: The Relation Between Cardiac Size and Cardiac Output per Minute Following the Administration of Digitalis in Dogs in Which the Heart Is Enlarged, J. Clin. Investigation **6**:79 (Aug.) 1928.

5. Burwell, C. S.; Neighbors, DeW., and Regen, E. M.: The Effect of Digitalis upon the Output of the Heart in Normal Man, J. Clin. Investigation **5**:125 (Dec.) 1928.

6. Harrison, T. R., and Leonard, B. W.: The Effect of Digitalis on the Cardiac Output of Dogs and Its Bearing on the Action of the Drug in Heart Disease, J. Clin. Investigation **3**:1 (Oct.) 1926.

7. Christian, H. A.: The Use of Digitalis Other Than in the Treatment of Cardiac Decompensation, J. A. M. A. **100**:789 (March 18) 1933.

8. Criteria for the Classification and Diagnosis of Heart Disease, ed. 2, New York, New York Tuberculosis and Health Association, 1929.

9. Experience with this particular "batch" showed that this amount was required regardless of body weight to slow the rapid ventricular rate in the presence of auricular fibrillation to around 70 per minute when given within twenty-four hours; it was considered as the "digitalizing" amount (unpublished data).

prepared and standardized by the American Heart Association. To all the patients the total amount was distributed during the day in approximately the same fashion, as follows: 0.8 Gm. at 8 or 9 a. m., 0.5 Gm. at noon or 1 p. m., 0.3 Gm. at 4 p. m. and 0.2 Gm. at 8 or 9 p. m. And finally, in the third place, observations were made at the same time with respect to the giving of digitalis: On the first day (see section on methods) observations on the circulation were made. On the next day digitalis was given; the first dose was administered early in the morning and the total amount by evening. On the next day, twenty-four hours after treatment with digitalis was started, observations were repeated and then again twenty-four or forty-eight hours later and in certain cases at still longer intervals. Since our other observations demonstrated that the early effects of digitalis were important, we made measurements twenty-four hours after use of the drug had been started. [1]

In addition to observations relating to rheumatic heart disease (cases 1 to 13, inclusive), data were also obtained concerning patients with hypertensive (case 14), arteriosclerotic (cases 15 and 16) and syphilitic (case 17) heart disease.

Methods.—The methods and plan of procedure used in making these observations, as well as those to be reported in our next paper,[2] were as follows:

All observations were made in the morning while the patient was in a basal metabolic state. Measurements of the cardiac output were made by the acetylene method, three samples of gas being taken, as recommended by Grollman [10] in his book entitled "The Cardiac Output of Man in Health and Disease," and as further elaborated by Grollman, Friedman, Clark and Harrison.[11] During this measurement the patient sat in a steamer chair (at an angle of 135 degrees) with the legs extended. Each patient was made familiar with and trained to carry out the procedures beforehand. While he was resting quietly, the radial pulse was counted at intervals of five minutes. At the end of one-half hour the acetylene-air-oxygen mixture was rebreathed. The amount of gas in the "rebreathing bag" was adjusted to the amount the patient could take satisfactorily. Three samples of gas were obtained during each period of rebreathing for estimation of the arteriovenous oxygen difference. Three periods of rebreathing were carried out to make certain that mixing was secured; one, two or all sets were analyzed. Shortly afterward the oxygen consumption was measured with a Benedict-Roth spirometer. After a short pause the vital capacity was measured, and the height and the weight were recorded. Then the patient rested again, this time by lying down. In succession, sufficient time being allowed between each procedure for the patient to return to a basal metabolic state, an electrocardiogram was taken, the

10. Grollman, A.: The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C. Thomas, Publisher, 1932, p. 73.

11. Grollman, A.; Friedman, B.; Clark, G., and Harrison, T. R.: Studies in Congestive Heart Failure: XXIII. A Critical Study of Methods for Determining the Cardiac Output in Patients with Cardiac Disease, J. Clin. Investigation **12**: 751 (Sept.) 1933.

arm to tongue circulation time recorded, the venous pressure estimated and the blood pressure measured; finally, the basal state still being maintained, a roentgenogram of the heart was made at a distance of 2 meters.

The arm to tongue circulation time was estimated by the use of decholin sodium; 5 cc. of a 20 per cent solution was injected rapidly (one to two seconds) through an 18 gage needle into an antecubital vein while the patient was lying quietly in a supine position. This was repeated one and one-half minutes after the response to the first test had been elicited. The time was recorded from the beginning of the injection until the patient perceived the bitter taste. The injection time was also recorded; since, however, the response may come with a minimal amount of the drug, the time which we used was measured from the start rather than from the conclusion of the injection.

The venous pressure was measured by the direct method,[12] a large antecubital vein being used and the arm being placed on a level with the right auricle. The apparatus consisted of an L tube of glass attached to a three way stopcock, a syringe and an 18 gage needle. The apparatus was filled with a sterile normal solution of sodium chloride, venipuncture was performed and the direct pressure readings were recorded. Normal pressures with this apparatus range from 4 to 9 cm. of saline solution. The antecubital vein of one arm was reserved for the injection of decholin and that of the other arm for the measurement of venous pressure. In subsequent measurements the vein was entered at the site first punctured.

Roentgenograms of the cardiac silhouette were taken with the patient in the standing position, during full inspiration, at a distance of 2 meters.[13] Measurements of the cardiac area were carried out by the technic of Levy,[14] and estimations of volume were made as recommended by Bardeen.[15] The volumes recorded in table 1 were not multiplied by the constant which is included in Bardeen's formula. This was omitted in order to make our observations comparable to those of Starr.[16]

The work of the left ventricle per beat was calculated by making use of the formula [17] $W = QR + \frac{wV^2}{2g}$, in which W equals the work done per beat; Q equals the volume of blood expelled per beat; R equals the mean arterial blood pressure in millimeters of mercury times 13.6; V equals the velocity of blood in the aorta; w equals the weight of the blood, and g equals the acceleration due to gravity. The last part of the formula, $\frac{wV^2}{2g}$, was omitted.[16]

Observations.—According to the results obtained for 13 patients suffering from rheumatic heart disease, three groups were made with

12. Taylor, F. A.; Thomas, A. B., and Schleiter, H. G.: A Direct Method for the Estimation of Venous Pressure, Proc. Soc. Exper. Biol. & Med. **27**:867 (May) 1930.

13. The staff of the Roentgenologic Department of the New York Hospital cooperated in this investigation.

14. Levy, R. L.: The Size of the Heart in Pneumonia: A Teleoroentgenographic Study, with Observations on the Effect of Digitalis Therapy, Arch. Int. Med. **32**:359 (Sept.) 1923.

15. Bardeen, C. R.: Determination of the Size of the Heart by Means of X-Rays, Am. J. Anat. **23**:423 (March) 1918.

16. Starr, I., Jr.; Collins, L. H., Jr., and Wood, F. C.: Studies of the Basal Work and Output of the Heart in Clinical Conditions, J. Clin. Investigation **12**: 13 (Jan.) 1933.

17. Starling, E. H.: Principles of Human Physiology, ed. 6, Philadelphia, Lea & Febiger, 1933, p. 772.

respect to the effect of digitalis on the cardiac output: In 4 cases (case 1 to 4) its effect was to decrease the cardiac output (group 1) and in 3 (cases 5 to 7) to increase the cardiac output (group 2); finally, in 6 cases (cases 8 to 13) no change in cardiac output was observed (group 3).

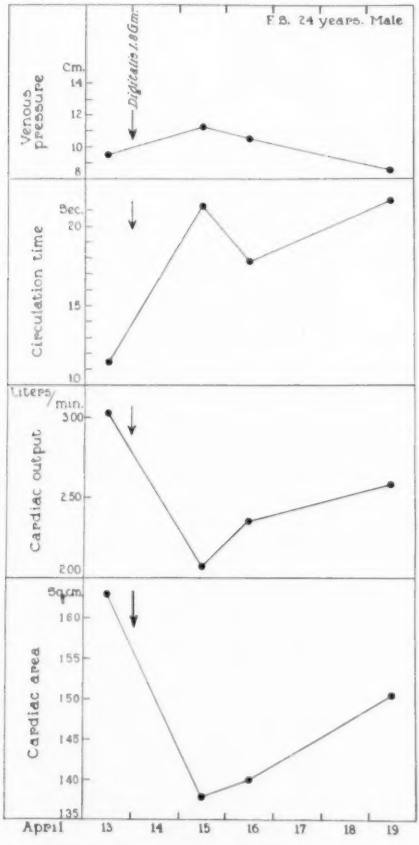

Fig. 1 (case 1).—The effect of digitalis on the cardiac output, cardiac size, venous pressure and circulation time of F. S., representing group 1.

Group 1. Decrease in Cardiac Output: Case 1 illustrates the effect of digitalis in this group of patients. After the administration of 1.8 Gm. of digitalis there occurred within twenty-four hours a decrease in cardiac output per minute (table 1 and figs. 1 and 2) and per beat, a

TABLE 1.—*Data Relating to the Effect of Digitalis in Seventeen Cases*

Case	Age	Sex	Date	Body Surface, Sq. M.	Oxygen Consumption, Cc. per Min.	Arteriovenous Oxygen Difference, Cc.	Cardiac Output, L. per Min.	Cardiac Output, L. per Sq. M. per Min.	Cardiac Area, Sq. Cm.	Cardiac Volume, Cc.†	Arterial Pressure, Mm. Hg	Circulation Time, Sec.
Rheumatic Heart Disease: Group 1. Decreased Cardiac Output												
1 F. S.	24	M	4/13/35	1.58	195	64.6	3.02	1.91	162.9	1,897	106/66	11.5
			4/14/35	....	....	....	....	....	.....	.....	.....	....
			4/15/35	1.58	180	86.9	2.07	1.31	138.0	1,483	112/76	21.3
			4/16/35	1.58	182	77.3	2.35	1.48	140.5	1,535	102/62	17.8
			4/19/35	1.58	187	72.4	2.58	1.63	150.5	1,690	132/70	21.6
2 A. G.	23	M	10/30/34	1.73	210	69.9	3.00	1.74	144.0	1,570	118/80	16.0
			11/12/34	1.75	214	69.7	3.06	1.79	141.9	1,530	118/74	18.5
			11/13/34	....	....	....	....	....	.....	.....	.....	....
			11/14/34	1.73	214	86.5	2.47	1.43	122.0	1,273	118/72	19.7
			11/16/34	1.72	214	88.6	2.41	1.40	117.6	1,170	118/72	20.0
			11/17/34	1.72	216	76.8	2.81	1.63	123.8	1,265	108/70	17.5
3 M. R.	32	F	4/ 4/34	1.45	158	89.6	1.76	1.21	154.4	1,745	115/55	....
			4/ 5/34	....	....	....	....	....	.....	.....	.....	....
			4/ 6/34	1.44	160	115.5	1.39	0.97	135.7	1,415	110/64	....
			4/ 7/34	1.44	160	109.3	1.46	1.01	130.2	1,350	105/65	....
			4/14/34	1.44	151	101.8	1.48	1.03	139.6	1,515	120/70	....
4 C. W.	25	M	12/ 7/35	1.92	290	73.4	4.00	2.03	273.6	4,120	102/54	24.0
			12/19/35	1.94	286	75.8	3.77	1.95	273.2	4,120	116/66	25.2
			12/20/35	....	....	....	....	....	.....	.....	.....	....
			12/21/35	1.90	267	89.5	2.98	1.57	248.9	3,580	108/65	25.7
			12/23/35	1.92	290	84.6	3.43	1.78	253.7	3,680	104/60	22.4
Group 2. Increased Cardiac Output												
5 E. P.	21	M	11/ 8/34	1.54	195	71.4	2.73	1.77	119.2	1,186	122/50	19.5
			11/ 9/34	....	....	....	....	....	.....	.....	.....	....
			11/10/34	1.55	185	60.4	3.07	1.98	99.8	910	120/50	14.7
			11/13/34	1.55	185	54.0	3.43	2.21	114.7	1,108	120/60	13.8
			11/15/34	1.55	190	60.4	3.14	2.03	114.8	1,108	120/50	15.3
6 M. C.	46	F	12/10/34	1.44	182	77.4	2.35	1.63	125.8	1,280	128/84	15.6
			12/11/34	....	....	....	....	....	.....	.....	.....	....
			12/12/34	1.44	177	77.0	2.30	1.60	131.0	1,365	120/68	17.6
			12/13/34	1.44	183	62.8	2.91	2.02	120.8	1,217	128/68	17.1
			12/18/34	1.44	191	67.2	2.84	2.00	111.7	1,076	118/69	20.7
7 R. D.	28	F	10/20/34	1.70	233	68.6	3.40	2.00	146.0	1,640	106/70	17.5
			10/27/34	....	....	....	....	....	.....	.....	.....	....
			10/22/34	1.70	218	47.8	4.56	2.62	132.4	1,380	108/66	13.7
			10/30/34	1.70	230	52.2	4.41	2.59	135.0	1,450	116/70	13.3
Group 3. No Change in Cardiac Output												
8 R. L.	21	M	4/ 6/35	1.75	234	70.9	3.30	1.89	120.6	1,220	120/64	17.2
			4/ 7/35	....	....	....	....	....	.....	.....	.....	....
			4/ 8/35	1.75	234	70.9	3.30	1.89	122.6	1,250	130/78	16.9
			4/ 9/35	1.76	230	74.0	3.11	1.77	119.3	1,200	124/70	17.4
9 J. F.	25	F	5/18/35	1.48	122	65.9	1.85	1.25	121.6	1,220	104.50	16.6
			5/19/35	....	....	....	....	....	.....	.....	.....	....
			5/20/35	1.49	131	67.1	1.96	1.31	120.5	1,208	104/68	15.5
			5/22/35	1.49	131	65.4	2.00	1.34	124.5	1,265	104/58	15.1
10 E. C.	19	F	3/18/35	1.66	195	82.8	2.36	1.42	106.9	1,040	104/10	10.7
			3/19/35	....	....	....	....	....	.....	.....	.....	....
			3/20/35	1.68	195	82.7	2.36	1.40	104.7	985	118/40	13.7
			3/21/35	1.68	189	82.2	2.30	1.37	101.6	825	120/ 0	12.3
11 A. M.	23	F	2/14/35	1.73	203	62.7	3.24	1.87	97.6	886	112/56	11.6
			2/15/35	....	....	....	....	....	.....	.....	.....	....
			2/16/35	1.71	205	61.9	3.31	1.94	95.3	837	120/50	13.7
12 J. S.	28	F	10/ 8/34	1.81	256	61.1	4.19	2.31	125.0	1,265	110/75	12.9
			10/ 9/34	....	....	....	....	....	.....	.....	.....	....
			10/10/34	1.81	256	60.9	4.20	2.32	125.6	1,280	122/66	11.5
			10/11/34	1.81	259	65.3	3.97	2.20	123.7	1,265	110/60	12.7
13 R. M.	21	F	9/19/34	1.46	185	....	....	....	180.6	2,210	130/70	....
			9/27/34	1.46	189	109.1	1.73	1.19	181.3	2,210	115/75	....
			9/29-30/34	....	....	....	....	....	.....	.....	.....	....
			10/ 1/34	1.44	198	106.0	1.82	1.26	175.6	2,120	90/70	....
			10/ 2/34	1.44	191	109.2	1.75	1.22	180.0	2,200	110/80	....
			10/ 3/34	1.44	180	101.5	1.76	1.22	172.9	2,080	100/70	....
			10/ 6/34	1.46	185	100.8	1.83	1.25	183.3	2,260	110/70	25.0

* In this table, as well as in table 2, the following symbols are used:[3] M. S., mitral stenosis; M. I., mitral insufficiency; A. S., aortic stenosis; A. I., aortic insufficiency; Enl. Ht., enlarged heart; Rt-I-V-HB, right intraventricular heart block. The roman numerals indicate the classification number.

† The volumes have not been multiplied by the constant included in Bardeen's formula, as stated in text.

Venous Pressure, Cm.	Vital Capacity, Cc.	Cardiac Rate, per Min.	Cardiac Output, Cc. per Beat	Work of Left Ventricle, Gm. M. per Beat	Digitalis, Gm.	Age at Which Rheumatic Infection Occurred, Yr.	Age at Which Cardiac Lesion Was Diagnosed, Yr.	Age at Onset of Symptoms, Yr.	Symptoms	Diagnosis	Red Blood Cell Count and Hemoglobin Value†
Rheumatic Heart Disease: Group 1. Decreased Cardiac Output											
9.5	4,400	72	42	49	...	8 chorea	Unknown	10	Occasional dyspnea	M. S.; M. I.; Enl. Ht.; I	4.4
....	.....	..	..	..	1.8	12 joints					80
11.2	4,100	72	29	37							
10.5	4,000	72	33	37							
8.5	4,200	60	43	59							
....	4,200	76	39	53	...	? 10	Unknown	23	Fatigue	M. S.; M. I.; Enl. Ht.; I	4.9
....	4,300	76	40	52							85
....	.....	..	..	..	1.7						
....	4,200	80	31	40							
....	4,250	80	30	39							
....	4,250	64	44	53							
....	2,100	60	29	34	...	Unknown	10	27	Dyspnea on exertion	M. S.; M. I.; Enl. Ht.; I	4.7
....	.....	..	..	..	1.6						100
....	2,180	65	21	25							
....	2,000	72	20	23							
....	2,200	58	26	34							
10.5	3,850	70	57	60.5	...	Unknown	12	3	Slight dyspnea	M. S.; M. I.; Enl. Ht.; I	5.4
8.8	4,100	70	54	66.8							94
....	.....	..	..	..	1.8						
8.6	4,100	64	47	52.4	0.2 q.d.§						
10.9	4,100	74	46	51.3							
Group 2. Increased Cardiac Output											
....	3,100	80	34	40	...	Unknown	Unknown	None	None	M. S.; M. I.; A. S.; A. I.; Enl. Ht.; IIA	5.0
....	.....	..	..	..	1.7						100
....	3,250	66	47	54	0.2 q.d.						
....	3,250	72	48	59							
....	3,200	64	49	56							
6.7	2,600	66	36	52	...	44	10	44	Slight dyspnea	M. S.; M. I.; A. S.; A. I.; Enl. Ht.; IIA	3.6
....	.....	..	..	..	1.8						79
5.6	2,550	62	37	47							
5.3	2,500	60	48	64							
5.3	2,600	59	48	61							
....	2,300	100	34	41	...	Unknown	24	24	Slight dyspnea	M. S.; M. I.; Enl. Ht.; IIA	91
....	.....	..	..	..	1.8						
....	2,450	82	56	68	0.2 q.d.						
....	2,500	82	54	66							
Group 3. No Change in Cardiac Output											
10.5	4,100	74	45	56	...	15 joints	Unknown	20	Slight dyspnea on exertion	M. S.; M. I.; A. I.; slightly Enl. Ht.; I	5.8
....	.....	..	..	..	1.8						102
8.3	4,030	72	46	65	0.3						
13.7	4,200	74	42	55							
6.8	2,800	70	26	27	...	Unknown	12	23	Dyspnea on exertion	M. S.; M. I.; A. S.; A. I.; slightly Enl. Ht.; I	4.8
....	.....	..	..	..	1.8						90
7.7	3,000	66	30	35	0.2 on						
7.8	3,000	78	27	30	May 21						
8.2	2,850	86	27	21	...	9 joints and chorea	9	None	None	M. S.; M. I.; A. S.; A. I.; slightly Enl. Ht.; I	4.8
....	.....	..	..	..	1.8						90
9.6	2,800	84	29	31		16 joints					
9.1	2,900	80	29	28		18 joints					
10.1	2,900	74	44	52	...	6 chorea	Childhood	22	Dyspnea on exertion	M. S.; M. I.; A. I.; Enl. Ht.; I or IIA	4.8
....	.....	..	..	..	1.8	15 chorea					88
9.5	2,250	72	46	58							
....	2,700	118	36	45	...	Unknown	24	Childhood	Slight dyspnea on exertion	M. S.; M. I.; slightly Enl. Ht.; I or IIA	75
....	.....	..	..	..	1.8						
....	2,950	106	40	51	0.2 q.d.						
....	2,850	100	40	47							
....	2,350	74	..	..	...	6 joints	6	12	Dyspnea on exertion	M. S.; M. I.; A. S.; A. I.; Enl. Ht.; IIA	4.1
....	2,600	72	24	31							85
....	.....	..	..	..	1.7						
....	2,525	70	26	29	0.2 q.d.						
....	2,500	64	27	35	0.1 on						
....	2,500	64	28	32	Oct. 5						
....	2,500	62	30	36							

† The values for red blood cells are given in millions; those for hemoglobin are given in percentages, 14.5 Gm. of hemoglobin being equivalent to 100 per cent.

§ When maintenance amounts of digitalis were given, the measurements were made in the morning as usual, and the maintenance dose of digitalis was given later in the day.

TABLE 1.—*Data Relating to the Effect of Digitalis in Seventeen Cases of Con*

Case	Age	Sex	Date	Body Surface, Sq. M.	Oxygen Consumption, Cc. per Min.	Arteriovenous Oxygen Difference, Cc.	Cardiac Output, L. per Min.	Cardiac Output, L. per Sq. M. per Min.	Cardiac Area, Sq. Cm.	Cardiac Volume, Cc.†	Arterial Pressure, Mm. Hg	Circulation Time, Sec.
Hypertensive Heart Disease												
14	62	F	3/11/36	1.61	143	65.9	2.17	1.35	118.7	1,180	150/80	15.6
A. G.			3/12/36	....	...	....	....	....	.....	.....	.....	...
			3/13/36	1.61	135	74.4	1.81	1.12	121.7	1,224	140/76	14.6
			3/14/36	1.61	120	68.2	1.76	1.10	113.0	1,095	160/80	17.0
Arteriosclerotic Heart Disease												
15	69	M	1/15/35	1.67	259	64.6	4.01	2.40	107.7	1,030	120/60	11.5
C. McA.			1/16/35	....	...	....	....	....	.....	.....	.....	....
			1/17/35	1.66	259	74.6	3.47	2.09	92.5	797	118/56	11.9
			1/19/35	1.66	267	60.7	4.40	2.65	100.7	927	124/70	11.5
16	58	M	10/29/35	1.59	160	72.9	2.20	1.38	139.0	1,403	122/82	27.0
J. S.			10/30/35	....	...	....	....	....	.....	.....	.....	....
			10/31/35	1.60	178	52.1	3.42	2.14	126.6	1,297	138/90	24.3
			11/ 6/35	1.57	174	48.3	3.60	2.29	105.1	982	129/78	20.4
Syphilitic Heart Disease												
17	48	M	10/15/34	1.75	227	64.1	3.54	2.02	.....	.....	118/50	13.2
H. W.			10/16/34	1.75	232	60.3	3.85	2.20	137.5	1,460	108/40	1.38
			10/17/34	1.75	222	60.1	3.69	2.10	138.5	1,485	118/46	12.8
			10/18/34	....	...	....	....	....	.....	.....	.....	....
			10/19/34	1.75	228	74.8	3.05	1.74	128.6	1,330	120/40	16.0
			10/23/34	1.75	220	73.5	2.99	1.71	127.3	1,295	130/50	15.1
			10/26/34	1.76	220	77.4	2.84	1.61	129.3	1,330	120/40	16.8

* In this table, as well as in table 2 the following symbols are used:[3] M. S., mitral stenosis; M. I., mitral insufficiency; A. S., aortic stenosis; A. I., aortic insufficiency; Enl. Ht., enlarged heart; Rt-I-V-HB, right intraventricular heart block. The roman numerals indicate the classification number.

† The volumes have not been multiplied by the constant included in Bardeen's formula, as stated in text.

TABLE 2.—*Data Relating to the Effect of Digitalis in Five Cases of*

Case	Age	Sex	Date	Body Surface, Sq. M.	Oxygen Consumption, Cc. per Min.	Arteriovenous Oxygen Difference, Cc.	Cardiac Output, L. per Min.	Cardiac Output, L. per Sq. M. per Min.	Cardiac Area, Sq. Cm.	Cardiac Volume, Cc.*	Arterial Pressure. Mm. Hg
18	73	M	3/ 5/35	1.80	205	97.6	2.10	1.17	224.1	3,055	140-130/ 76
H. O.			3/ 6/35	....	...	....	....	....	.....	.....	.....
			3/ 7/35	1.79	222	62.5	3.55	2.00	210.8	2,792	145/ 60
19	25	F	4/11/34	1.52	191	96.2	1.98	1.30	189.8	2,398	98/ 60
M. R.			4/20/34	1.52	180	98.2	1.83	1.20	194.4	2,472	98/ 60
			4/21/34	....	...	....	....	....	.....	.....	.....
			4/22/34	1.52	184	84.5	2.18	1.44	178.4	2,172	110/ 80
			4/27/34	1.48	172	83 6	2.06	1.39	185.1	2,315	98/ 60
20	44	F	10/25/34	1.47	218	125.6	1.74	1.18	136.1	1,450	150/100
C. C.			10/26/34	....	...	....	....	....	.....	.....	.....
			10/27/34	1.44	189	89.3	2.12	1.45	122.3	1,232	130/ 70
21	28	M	11/12/35	1.55	237	86.3	2.75	1.80	154.3	1,746	135/ 76
J. G.			11/13/35	....	...	....	....	....	.....	.....	.....
			11/14/35	1.55	228	81.0	2.81	1.80	157.8	1,805	150/ 78
			11/16/35	1.55	226	86.2	2.61	1.70	143.5	1,567	152/ 76
22	50	M	10/ 1/35	2.13	267	68 2	3.92	1.84	159.3	1,833	120/ 80
H. C.			10/ 2/35	....	...	....	....	....	.....	.....	.....
			10/ 3/35	2.13	267	66.1	4.04	1.90	153.0	1,726	118-110/ 84

* The volumes have not been multiplied by the constant included in Bardeen's formula, as stated in text.

† The values for red blood cells are given in millions; those for hemoglobin are given in percentages.

pensated Cardiac Disease Associated with Normal Rhythm—Continued*

Venous Pressure, Cm.	Vital Capacity, Cc.	Cardiac Rate, per Min.	Cardiac Output, Cc. per Beat	Work of Left Ventricle, Gm. M. per Beat	Digitalis, Gm.	Age at Which Rheumatic Infection Occurred, Yr.	Age at Which Cardiac Lesion Was Diagnosed, Yr.	Age at Onset of Symptoms, Yr.	Symptoms	Diagnosis	Red Blood Cell Count and Hemoglobin Value‡
					Hypertensive Heart Disease						
9.1	1,600	80	27	42	...	Unknown	Unknown	45	Slight dyspnea	Rt-I-V-HB; not Enl. Ht.; IIA	3.7 84
....	.....	..	..	..	1.8						
7.8	1,500	70	26	38							
8.8	1,350	66	27	44							
					Arteriosclerotic Heart Disease						
5.5	2,700	70	57	70	...	Unknown	Unknown	66	Slight dyspnea	M. I.; not Enl. Ht.; IIA	4.5 90
....	.....	..	..	..	1.8						
5.3	2,500	82	42	50							
5.8	2,500	72	61	80							
3.7	2,600	58	38	53	...	Unknown	Unknown	Unknown	Occasional paroxysmal tachycardia	None; not Enl. Ht.; IIA	4.9 100
....	.....	..	..	..	1.8						
4.9	2,700	56	61	94	0.2 q.d.						
3.8	2,900	64	56	79							
					Syphilitic Heart Disease						
....	4,100	74	48	55	...	Syphilitic infection at 22	Unknown	None	None	A. I.; Enl. Ht.; I	4.3 84
....	4,100	72	53	53							
....	4,250	74	49	55							
....	.....	..	..	..	1.8						
...	4,250	70	43	47	0.2 q.d.						
....	4,250	68	43	53							
....	4,200	64	44	48							

‡ The values for red blood cells are given in millions; those for hemoglobin are given in percentages, 14.5 Gm. of hemoglobin being equivalent to 100 per cent.

§ When maintenance amounts of digitalis were given, the measurements were made in the morning as usual, and the maintenance dose of digitalis was given later in the day.

Compensated Cardiac Disease Associated with Auricular Fibrillation

Circulation Time, Sec.	Venous Pressure, Cm.	Vital Capacity, Cc.	Cardiac Rate, per Min.	Cardiac Output, Cc. per Beat	Work of Left Ventricle, Gm. M. per Beat	Digitalis, Gm.	Diuresis	Diagnosis	Red Blood Cell Count and Hemoglobin Value‡
21.2	8.9	3,800	92	23	33.2	...	Not measured	M. S.; M. I.; Enl. Ht.; I	
...	.....	.....	...	..	.....	1.7			
....	8.2	3,800	70	51	71.4				
....	...	2,100	86	23	24.7	...	None	M. S.; M. I.; Enl. Ht.; IIA	4.2 90
....	...	2,310	106	17	18.5				
....	...	.....	...	..	.....	1.7			
.....	...	2,300	70	30	38.8	0.1 q.d.			
....	...	2,700	70	30	32.2				
17.0	...	1,900	142	12	20.7	...	None	M. S.; M. I.; slightly Enl. Ht.; IIA	5.0 100
....	...	.....	...	..	.....	1.8			
10.0	...	2,100	92	23	31.3				
19.9	9.1	2,750	66	42	60.5	...	None	M. S.; M. I.; Enl. Ht.; IIA	
....	...	.....	...	..	.....	1.8			
21.2	5.9	2,830	52	54	83.7	0.1 q.d.			
22.1	6.3	2,900	50	52	80.6				
18.5	8.3	3,300	88	45	61.2	...	None	Arteriosclerosis; Enl. Ht.; IIA	5.2 100
....	...	.....	...	..	.....	1.8			
18.8	8.9	3,600	89	52	70.0				

decrease in cardiac size, slowing of the circulation time and no essential change in venous pressure. Reversion toward predigitalis levels occurred as the digitalis effect wore off. Results similar to these were observed in 3 other patients (cases 2 to 4) suffering from rheumatic heart disease, as well as in 1 with hypertensive (case 14), 1 with arteriosclerotic (case 15) and 1 with syphilitic (case 17) involvement (table 1).

Group 2. Increase in Cardiac Output: Case 5 illustrates the effect of the drug in this group. Twenty-four hours after the giving of 1.7 Gm. of digitalis there occurred an increase in cardiac output per minute and

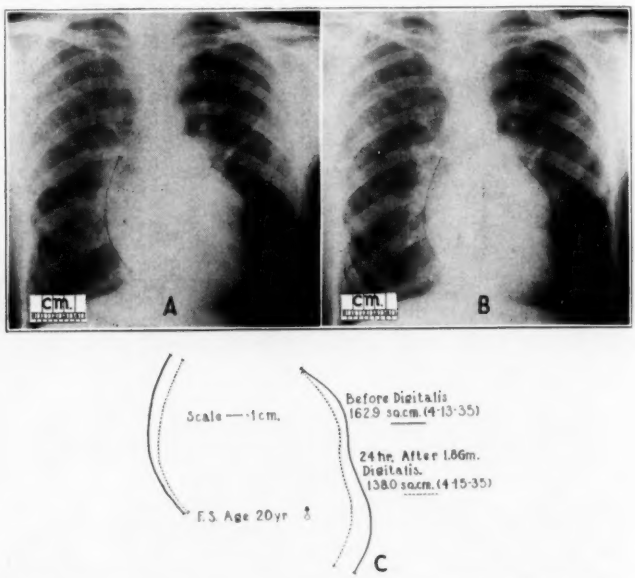

Fig. 2 (case 1).—The change in the size of the heart after the administration of 1.8 Gm. of digitalis. *A* was taken (April 13, 1935) before and *B* was taken (April 15) twenty-four hours after the administration of the drug. In *C* the outlines of the heart traced from *A* and *B* are superimposed.

per beat, a decrease in the size of the heart and a shortening of the circulation time (table 1 and figs. 3 and 4). In this patient these trends were maintained with continuation of the drug. The results in 2 other patients suffering from rheumatic (cases 6 and 7) as well as 1 (case 16) suffering from arteriosclerotic heart disease followed a similar pattern (table 1).

Group 3. No Change in Cardiac Output: Case 8 illustrates the effect of digitalis in this group of 6 patients (cases 8 to 13, table 1). The

giving of 1.8 Gm. of digitalis to this patient was associated with no significant change in cardiac output, cardiac size, circulation time or venous pressure (table 1 and figs. 5 and 6), although changes in the T wave of the electrocardiogram were recorded.

II. OBSERVATIONS RELATING TO PATIENTS EXHIBITING AURICULAR FIBRILLATION

The notion is current that the action of digitalis is not the same when auricular fibrillation is present as it is when regular sinus rhythm is

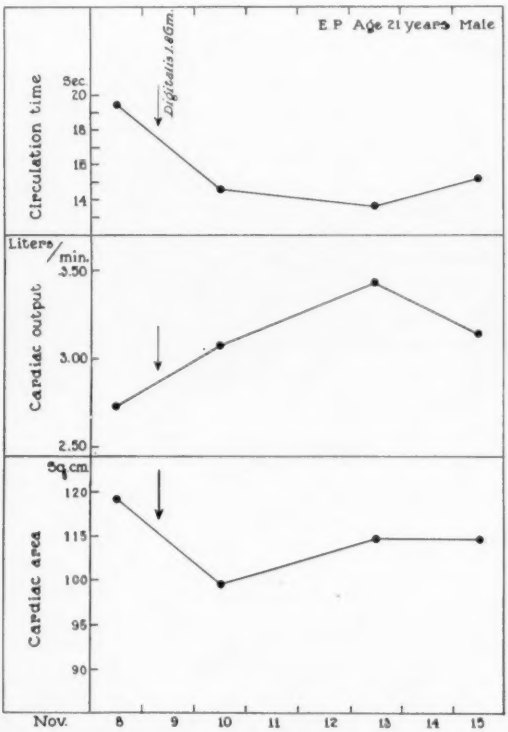

Fig. 3 (case 5).—The effect of digitalis on the cardiac output, cardiac size and circulation time of E. P., representing group 2.

present. Our earlier observations [1] indicated that the action of the drug is similar under these two conditions. Our present observations were designed to yield additional data on this subject.

Observations were made on 5 patients exhibiting auricular fibrillation who satisfied the following criteria: (*a*) They suffered from

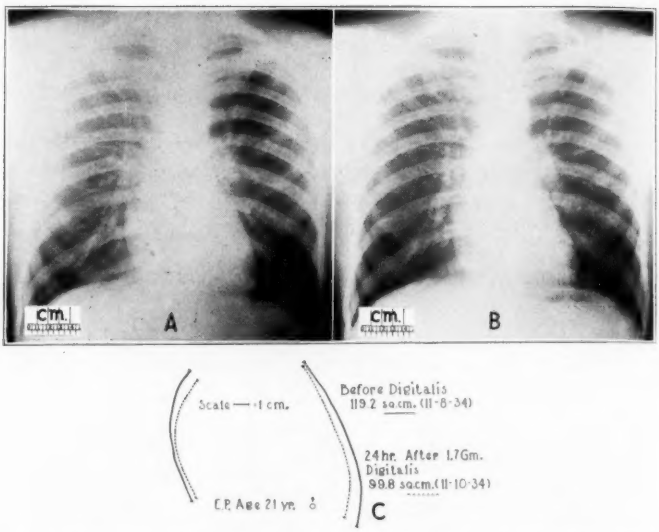

Fig. 4 (case 5).—The change in the size of the heart. *A* was taken (Nov. 8, 1934) before and *B* (November 10) twenty-four hours after digitalis was given. In *C* the outlines of the heart traced from *A* and *B* are superimposed.

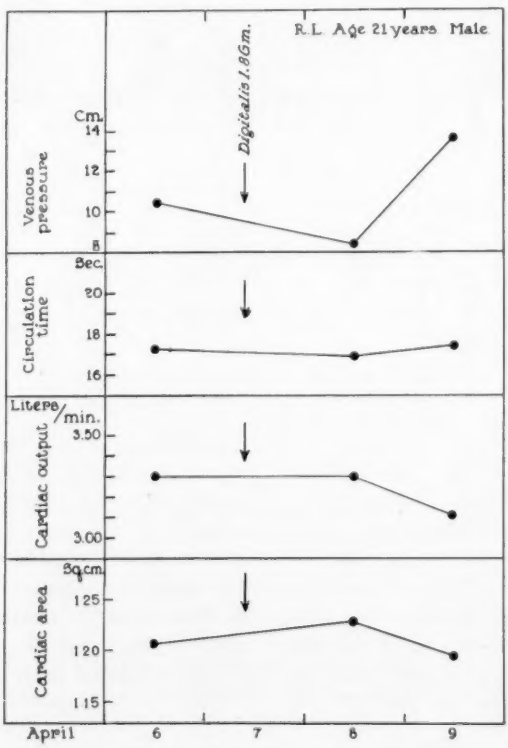

Fig. 5 (case 8).—The effect of digitalis on the cardiac output, cardiac size, venous pressure and circulation time of R. L., representing group 3.

organic heart disease, and (*b*) they did not exhibit signs of congestive heart failure at the time these observations were made. To each was given within twenty-four hours the same amount of digitalis (1.7 to 1.8 Gm.) from the same batch as that given to the groups of patients with normal sinus rhythm as well as to those suffering from congestive heart failure.[2a] The plan of the observations was similar to that already outlined in the section on methods.

Observations.—Before digitalis was given the cardiac output of all the patients was less than the calculated normal output (table 2). In 3 cases (cases 18 to 20) the giving of digitalis in the manner described

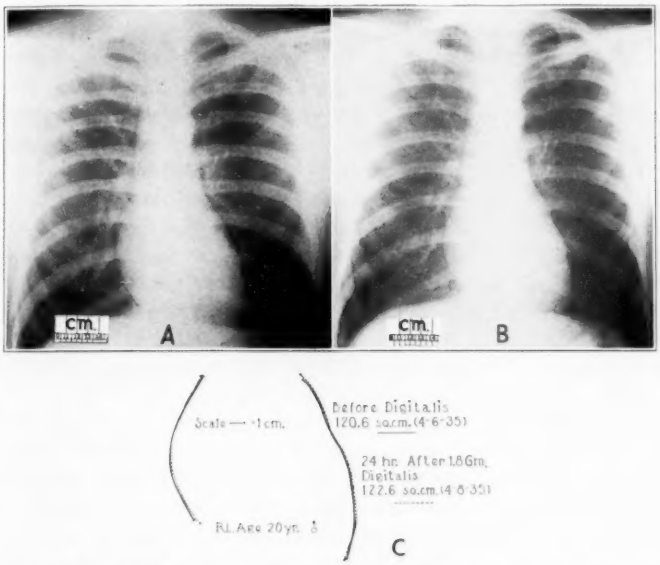

Fig. 6 (case 8).—Roentgenograms of R. L. *A* was taken (April 6, 1935) before and *B* (April 8) twenty-four hours after digitalis was given. In *C* the outlines of the heart traced from *A* and *B* are superimposed.

resulted in twenty-four hours in an increase in cardiac output per minute and per beat (table 2) and a decrease in the size of the heart. The circulation time was shortened in 1 case in which it was measured (case 20). No change in the venous pressure occurred in the 1 case in which it was recorded (case 18). In 2 other cases (cases 21 and 22, table 2) twenty-four hours after the drug was given the cardiac size was unchanged, and the cardiac output was unchanged, but the cardiac output per beat was increased. No significant changes in circulation time and venous pressure occurred.

COMMENT

The administration of digitalis in the same amounts to 13 patients with rheumatic heart disease for whom approximately the same functional classification could be made (group I or group II A) and the making of observations at the same time with respect to the giving of the drug showed an increase in output in certain cases, a decrease in others and no change in still others. We should be at a loss to account for these differences did we not have data relating to cardiac size, circulation time and venous pressure. One result of the action of digitalis appeared to be common to two groups, namely, a decrease in cardiac size; when the cardiac size decreased, the cardiac output altered; when the cardiac size remained unchanged, the cardiac output likewise remained unchanged. Furthermore, a decrease in cardiac size in certain instances was associated with a decrease in cardiac output and in others with an increase in cardiac output. Most of the patients showing a decrease in cardiac output showed slowing of the circulation time, just as most of those having an increase in cardiac output showed shortening of the circulation time, in short, acceleration of the blood flow. It is recalled that a decrease in cardiac output and in cardiac size has been observed (Stewart and Cohn) in normal human beings,[1] in normal dogs [3] and in dogs having large hearts [4] when digitalis has been given. Moreover, an increase in cardiac output and a decrease in cardiac size have been observed [1] and further confirmed by us [2a] (Stewart, Deitrick, Crane, and Wheeler) in patients suffering from congestive heart failure. The effect of the size of the heart under the influence of digitalis on the volume of blood pumped by it is given added significance by the observation that when the cardiac size was unaltered the cardiac output was also unchanged. The effects, an increase or decrease in output, became less as the drug was excreted, or they remained approximately the same if its use was continued. Moreover, the few observations relating to other etiologic types indicates that the effects which have been described are not confined to cases of rheumatic heart disease. The effect on cardiac size appears at times to outweigh an effect on contraction which has been demonstrated in man and in dogs (Cohn and Stewart [18]). Though the extent of ventricular contraction might be increased, the decrease in size was sufficient in some instances to make the output smaller.

These observations strengthen our notion that in normal persons as well as in the patients with cardiac disease now described, a decrease in cardiac output is a consequence of the fact that the heart has been made

18. Cohn, A. E., and Stewart, H. J.: Evidence That Digitalis Influences Contraction of the Heart in Man, J. Clin. Investigation **1**:97 (Oct.) 1924; footnotes 3 and 4.

smaller by an action of the drug on it. It does not seem possible to attribute the decrease in output in these instances in man to diminished venous filling, a consequence of constriction of the hepatic veins (Dock and Tainter [19]); in the first place, a fall in venous pressure did not occur; in the second place, the decrease in venous pressure which Dock and Tainter observed in dogs was transient, a matter of minutes (under thirty minutes in most instances), but the effects we observed on size and output were present for a matter of days; in the third place, we were unable to observe a change in the size of the liver. It may be recalled that Tainter and Dock [19b] showed that giving digitalis to dogs results, by its action on the hepatic veins, in an increase in the volume of the liver. The output of blood from the heart of 1 of our patients (case 4, table 1) decreased from 3.77 liters per minute to 2.98 liters per minute, twenty-four hours after 1.8 Gm. of digitalis was given, in short, a falling off of one quarter of its minute volume. Nevertheless, the size of the liver in roentgenograms did not increase. When congestive heart failure supervened, two years later, the liver became swollen and tender, indicating that it was capable of distention. In none of these patients showing a decrease in output was there clinical evidence of enlargement of the liver after digitalization. Finally, in the fourth place, we may emphasize the argument made in an earlier paper (Stewart and Cohn [1]) that constriction of the hepatic veins in man, even though their lumens were reduced to zero, would be insufficient to account for the magnitude of decrease in cardiac output which we have recorded.

If digitalis makes the heart a smaller pump and if it pumps a smaller amount of blood, the issue might be raised that the venous pressure should become elevated; in short, that the resulting situation would resemble the defect exhibited in chronic constrictive pericarditis. In the case of the latter, our own observations,[20] as well as those of Burwell and his associates,[21] have shown interference not only with filling of the heart, since the heart in diastole is unable to stretch the

19. (*a*) Dock, W., and Tainter, M. L.: Circulatory Changes After Full Therapeutic Doses of Digitalis, with a Critical Discussion of Views on Cardiac Output, J. Clin. Investigation **8**:467 (April) 1930. (*b*) Tainter, M. L., and Dock, W.: Further Observations on the Circulatory Actions of Digitalis and Strophanthus, with Special Reference to the Liver, and Comparisons with Histamine and Epinephrine, ibid. **8**:485 (June) 1930.

20. Stewart, H. J., and Heuer, G. J.: Measurements of the Circulation in Constrictive Pericarditis Before and After Resection of the Pericardium, Tr. A. Am. Physicians **52**:342, 1937.

21. Burwell, C. S., and Strayhorn, W. D.: Concretio Cordis: I. A Clinical Study with Observations on the Venous Pressure and Cardiac Output, Arch. Surg. **24**:106 (Jan.) 1932. Burwell, C. S., and Flickinger, D.: Obstructing Pericarditis: Effect of Resection of the Pericardium on the Circulation of a Patient with Concretio Cordis, Arch. Int. Med. **56**:250 (Aug.) 1935.

fibrous sac, but also with emptying, since the heart cannot contract adequately. That filling of the digitalized heart is not compromised and that it receives all the blood presented to it is shown by the absence of a rise in venous pressure. In man piling up of blood on the venous side has not been observed as a consequence of giving digitalis. What the distribution of the volume of circulating blood may be is not known.

In this connection there remains to be considered the data reported by Rytand.[22] He observed the effect of digitalis on the venous pressure of human beings and came to the conclusion that a decrease in cardiac output was a consequence of a fall in venous pressure. In the first place, not only were the changes which he observed in venous pressure sometimes above and sometimes below the initial level in the same patient, but they were of small magnitude. They do not appear to us to be significant, for we have observed changes greater than these in the venous pressure from day to day in a normal person without medication under basal conditions.[23] Even though a decrease had been a consistent finding, the slight change which he observed does not appear to be of sufficient magnitude to account for the marked change in cardiac output and in size which we have found. In the second place, since he did not make observations on the cardiac output of his subjects, it is not possible to say what changes in cardiac output, if any, occurred. Moreover, no observations were made of any other functions, such as those shown in electrocardiograms, by which to establish objectively one effect of digitalis with which to correlate the alteration in venous pressure. And, finally, he has treated data from our observations [1] in a fashion which is open to question. He plotted our figures for cardiac output against his figures for venous pressure and concluded that the decrease in cardiac output was due to a fall in venous pressure. However, examination of our charts in which the raw data were plotted [1] showed that in not a single case was parallelism revealed between the decrease in cardiac output and cardiac size, on the one hand, and the decrease in venous pressure, on the other. Obviously a relation which was not revealed in a single one of our cases cannot serve as a basis for arriving at the generalization he has made.

There appears to be no reason for changing our original view that the decrease in cardiac output which we observed was associated with a decrease in the size of the heart. Indeed, the data now recorded strengthen it.

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22. Rytand, D. A.: The Effect of Digitalis on the Venous Pressure of Normal Individuals, J. Clin. Investigation **12**:847 (Sept.) 1933.

23. Stewart, H. J., and Watson, R. F.: Studies of the Circulation in Athletes, to be published.

The effect of digitalis on the work of the left ventricle per beat was calculated. The opinion has been expressed (Stewart and Cohn [1]) that the explanation of the increase in cardiac output with the decrease in cardiac size as a consequence of the giving of digitalis is to be found in Starling's [24] "law of the heart." Starr and his associates [25] have presented since then data indicating that this "law" applies to basal cardiac work in human beings as well as to that in the heart-lung preparation, since they found that the work of the left ventricle which is maintaining an adequate circulation bears a linear relation to the size of the heart. From their data they have defined a zone of normal circulatory function. In a manner similar to theirs we have plotted cardiac volumes as abscissas and gram meters of work of the left ventricle per beat as ordinates (table 1 and figs. 7 and 8). The values for only 5 of the 17 patients with normal rhythm fell outside the zone of normal circulatory function, below line *CD,* in an area indicating that the work of the heart was not commensurate with its size. When these 5 were given digitalis, not all could be assigned to a single group (groups 1, 2 or 3), as might have been expected, but some belonged to each of the three groups indicated. A distinction so far as response to digitalis was concerned could not be made on this basis. In all the 5 cases mentioned, digitalis raised the values appreciably closer to or into the zone of normal circulatory function, whether the cardiac output was increased, decreased or unchanged by the drug. Moreover, in none of the 17 cases was the cardiac efficiency with the patient at rest diminished by the giving of digitalis, but the values moved closer to the best line of regression, *AB.* Though there were the three results with respect to cardiac output per minute, it appears that there is a common underlying effect of the drug in all these cases; namely, the work of the heart per beat was brought in all instances more in line with the work expected of it for its volume. Basis is thereby afforded Christian's recommendation of giving digitalis to patients exhibiting organic valvular disease before the occurrence of congestive heart failure.[7] A decision as to whether or not digitalis is of "benefit" in the long run in such cases will depend on clinical observations regarding the life span and the state of well-being of a large series of patients during treatment as compared with observations on a group of untreated patients to whom the drug is not administered until congestive heart failure supervenes. After the giving of digitalis the visible and

24. Starling, E. H.: The Linacre Lecture on the Law of the Heart, Given at Cambridge, 1915, London, Longmans, Green & Co., 1918.

25. Starr, I., Jr.; Donal, J. S.; Margolies, A.; Shaw, R.; Collins, L. H., and Gamble, C. J.: Studies of the Heart and Circulation in Disease: Estimations of Basal Cardiac Output, Metabolism, Heart Size, and Blood Pressure in Two Hundred and Thirty-Five Subjects, J. Clin. Investigation **13**:561 (July) 1934. Starr, Collins and Wood.[16]

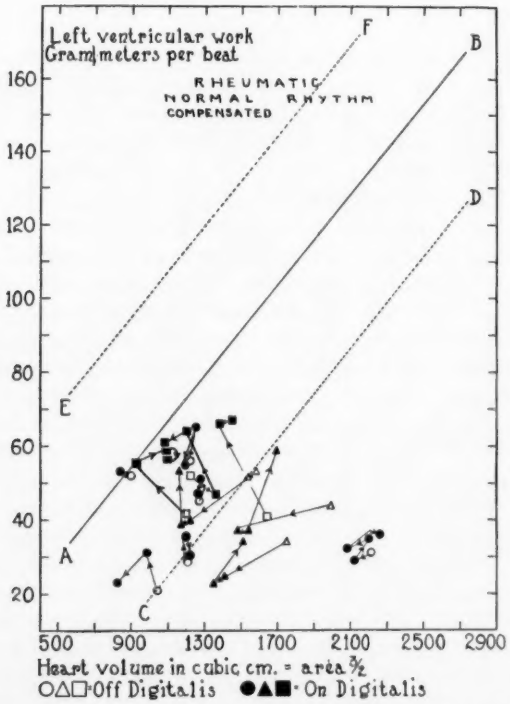

Fig. 7.—The work of the left ventricle per beat and the cardiac volume. The data from table 1 relating to the work of the left ventricle per beat in rheumatic heart disease particularly (cases 1 to 3 and 5 to 13) are plotted against the corresponding cardiac volumes. Line *AB* represents the best line, "the regression of the work on the area," defined by Starr, Collins and Wood [16] (and illustrated in their figure 2) on the basis of a statistical treatment of data for a control group of patients. Lines *CD* and *EF* were placed by these authors at a distance of twice the standard deviation from *AB*. It appears from their observations that a patient whose values fall within zone *CD-EF* has a normal circulatory function, that is to say, the work of the heart is commensurate with its size; on the other hand, they found that the values relating to patients who had suffered from cardiac decompensation fell in a zone below *CD*. In our series, the values for all the patients except 1 (case 5; the data relating to case 4 were not plotted) fell in the zone representing normal circulatory function. The triangles represent patients whose cardiac output decreased (group 1); the squares, those whose output increased (group 2), and the circles, those whose output did not change (group 3) after the giving of digitalis. In this figure as well as in figures 8 and 9 open symbols indicate "before" and closed ones "after" the giving of digitalis. Arrows point from the first observations to those made later. All the observations made after digitalis was given are recorded by solid symbols, whether the use of the drug was continued after the digitalizing amount or not, since the amount of exertion could not be ascertained. The values for C. W. (case 4) were not plotted on the chart because they fell so far below line *CD* and to the right that it did not seem worth while to increase the dimensions of the chart in order to include him. In all instances the giving of digitalis made the values for the patient take up a more advantageous position on the chart.

the palpable apex thrust became more forceful, and on auscultation the heart appeared to be contracting more forcefully and emptying more completely.

In the group of patients with auricular fibrillation the work of the left ventricle of the heart per beat was increased also in each instance by the giving of digitalis, so that the work came more nearly in line with

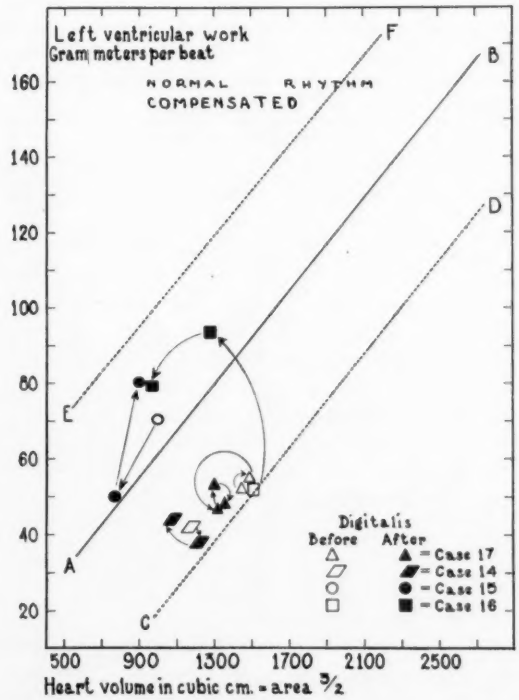

Fig. 8.—In this figure the work of the left ventricle per beat is plotted against the cardiac volume in cases 14 to 17; all the values fell in the zone of normal circulatory function; nevertheless, the giving of digitalis raised each to a more advantageous position.

that expected of the heart for its size. The values for 3 patients (cases 20 to 22) in this group moved up into the zone of normal circulatory function, *CD-EF*, during rest (fig. 9), and those for 2 others (cases 18 and 19) moved nearer the best line, *AB*.

We have seen that the results of giving digitalis to patients suffering from compensated heart disease are not predictable, for in some cases the heart behaved like a normal heart, a decrease in the size of the

pump being associated with a decrease in the output, and in other cases it behaved like the dilated heart of a patient suffering from heart failure, restoration of the cardiac size to a more optimal level resulting in an increase in output.[1] The functional state of the heart in these cases could not be distinguished clinically. Moreover, there were no similar features for each group so far as concerned the level of cardiac output, cardiac size or circulation time before digitalis was given, which made them fall later into these groups; nor did they fall together with respect to the work of the heart. Group 3 is puzzling, for it may be recalled

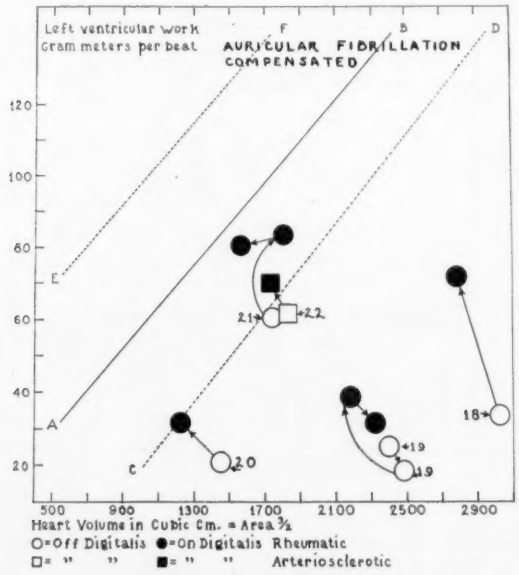

Fig. 9.—In this figure the work of the left ventricle per beat is plotted against the cardiac volume in cases 18 to 22, cases in which there was auricular fibrillation; after digitalis was given the values for 3 moved up into the zone of normal circulatory function, and those for the other 2 moved closer to the line *CD*.

that giving digitalis to these patients did not alter the cardiac output per minute, nor did it alter the cardiac size, circulation time or venous pressure. Nevertheless, a digitalis effect was present, for the T wave of the electrocardiogram showed characteristic changes.[26] Various factors

26. Cattell, McK., and Gold, H.: The Influence of Digitalis Glucosides on the Forces of Contraction of the Mammalian Cardiac Muscle, J. Pharmacol. & Exper. Therap. **62**:116 (Jan.) 1938.

about which we have no data must have neutralized each other so that a change in size and output did not occur. This group 3 exhibited in a fashion similar to that exhibited by the other two increase in the work of the heart per beat. Although the observations were confined largely to subjects with rheumatic heart disease, the few observations made on subjects with other etiologic types of heart disease showed that the phenomena described are not confined to the category of rheumatic heart disease.

Furthermore, observations on the patients exhibiting auricular fibrillation showed that the effect of the action of digitalis on them was not different from the effect on those exhibiting a normal sinus mechanism. Those having an increase in output after digitalization were found to show a decrease in the size of the heart, and those having no change in output showed no significant change in the size of the heart, observations which parallel those made for patients with normal sinus rhythm. Once again it is demonstrated that the effect on the size of the heart is pertinent. Though the cardiac output per minute in 2 cases was unchanged, the output per beat was increased, owing in part to slowing of the heart rate and in part probably to an increase in ventricular contraction.[18] As we have already pointed out, the phenomenon common to all groups—whether the output was increased, decreased or unchanged and whether the rhythm was regular or that of auricular fibrillation—was that the work of the heart per beat was made commensurate (or more nearly so) with its size.

The bearing on this subject of the recent observations of Cattell and Gold[26] relating to the effect of digitalis on systolic tension is discussed in our paper dealing with uncompensated heart disease.[2n]

SUMMARY

We gave 1.6 to 1.8 Gm. of digitalis within twenty-four hours to 13 patients suffering from rheumatic heart disease and to 4 others with arteriosclerotic, hypertensive or syphilitic heart disease. In all cases there was compensation, and a normal sinus mechanism was exhibited. In addition to clinical studies of these patients, special observations were made of the cardiac output, cardiac size, circulation time and venous pressure. In all cases the T wave and the R-T segment of the electrocardiogram showed the changes characteristic of a digitalis effect. It was found that 7 patients showed a decrease in cardiac output and a decrease in cardiac size, 4 patients showed an increase in cardiac output and a decrease in cardiac size and 6 patients showed no change in cardiac output and in cardiac size. In short, in some instances when the heart was made smaller, the cardiac output increased, and in others it decreased. In the former cases the heart behaved like a failing heart (part II of

our previous study [1])[2a] and in the latter cases like a normal one (part I of our previous study [1]). We were unable to predict beforehand which effect would be produced.

The results in 5 patients exhibiting auricular fibrillation were not different from those encountered in those with normal sinus rhythm—a decrease in cardiac size was associated with a decrease in cardiac output, and an unchanged cardiac size was associated with an unchanged cardiac output.

Digitalis has four effects on the heart which may be recorded clinically: (1) an effect on contraction,[18] namely, an increase; (2) an effect on size (Stewart and Cohn [27] and observations in this paper), namely, a decrease; (3) an effect on the cardiac rate, namely, a decrease; [1] and (4) an effect on the electrocardiogram,[28] indicating an effect on the cardiac muscle. The cardiac output which results is different, depending on the individual heart, that is to say, whether it is dilated or not.

A few observations on patients with heart disease due to other etiologic factors showed that these phenomena are not confined to those with rheumatic involvement.

There is one phenomenon which is common to all groups: The giving of digitalis increases the work accomplished by the heart per beat, whether its action is to increase or to decrease the output or to leave it unaltered and whether the rhythm is regular or that of auricular fibrillation. As a consequence, work becomes more nearly appropriate for the size of the organ. Some basis is afforded Christian's suggestion of giving digitalis to the patient suffering from organic heart disease even though he shows no significant failure.

These studies yield additional evidence that a decrease in cardiac output which follows the giving of digitalis to human beings (normal and those having organic heart disease without congestive heart failure) is not a consequence of diminished venous return but a consequence, so far as we can now ascertain, of a decrease in the size of the heart due to the action of digitalis on it.

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27. Stewart and Cohn.[1] Cohn and Stewart.[3,4]

28. Stewart, H. J., and Watson, R. F.: The Effect of Digitalis on the Form of the Human Electrocardiogram, with Special Reference to Changes Occurring in the Chest Lead, Am. Heart J., to be published.

ACTION OF DIGITALIS IN UNCOMPENSATED HEART DISEASE

HAROLD J. STEWART, M.D.

JOHN E. DEITRICK, M.D.

NORMAN F. CRANE, M.D.

AND

CHARLES H. WHEELER, M.D.

NEW YORK

It has been demonstrated as a fact that digitalis decreases the cardiac output (Stewart and Cohn [1] and Burwell, Neighbors and Regen [2]) and the cardiac size in normal human beings (Stewart and Cohn [1]). It was found (Stewart and Cohn [1]) that the cardiac output was diminished and the heart dilated in the presence of congestive heart failure and that the administration of digitalis in these instances increased the cardiac output and decreased the cardiac size. We (Stewart, Crane, Deitrick and Thompson [3]) have recently published data relating to patients suffering from organic heart disease, without congestive heart failure, with normal rhythm. In certain of these cases the behavior of the heart was normal; in others the behavior was like that of a failing heart. In addition, we [3] have shown in these later observations that digitalis increased the work of the heart per beat. Moreover, the action of the drug was the same whether the rhythm was that of a normal sinus mechanism or of auricular fibrillation.[3]

In rounding out our study of the action of digitalis we wished to investigate further its action in the presence of congestive heart failure when a normal sinus mechanism was exhibited as well as when auricular

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From the New York Hospital and the Department of Medicine, Cornell University Medical College.

An abstract of these studies was presented before the American Heart Association, Kansas City, Kan., May 12, 1936.

1. Stewart, H. J., and Cohn, A. E.: III. Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart, J. Clin. Investigation **11**:917 (Sept.) 1932.

2. Burwell, C. S.; Neighbors, DeW., and Regen, E. M.: The Effect of Digitalis upon the Output of the Heart in Normal Man, J. Clin. Investigation **5**:125 (Dec.) 1927.

3. Stewart, H. J.; Crane, N. F.; Deitrick, J. E., and Thompson, W. P.: Action of Digitalis in Compensated Heart Disease, Arch. Int. Med., this issue, p. 547.

fibrillation was present, since there are still differences of opinion as to the action of the drug in the presence of a failing heart. These data form the basis of this paper.

I. OBSERVATIONS ON PATIENTS EXHIBITING NORMAL SINUS RHYTHM

Plan of Observations.—In order to make our observation comparable not only within this group but also with respect to the observations on the other groups studied,[3] we maintained the following uniform conditions:

(*a*) All the patients were at rest in bed during the period of these observations; (*b*) all observations were made in the morning while the patients were in a basal metabolic state; (*c*) all the patients exhibited a regular sinus mechanism; (*d*) all the patients were given the same amount of the drug,[4] namely, 1.7 to 1.8 Gm., within twenty-four hours, distributed in the same fashion; the digitalis was of the same "batch" as that used in the former observations; [3] (*e*) studies were made the day before and again twenty-four hours after the giving of digitalis and then again at varying intervals later. We adhered to making observations twenty-four hours after giving the drug because our observations have shown that the early effects of digitalis are important. In those instances in which the use of digitalis was continued, the observations were made as usual in the morning, and the maintenance dose of the drug was given later in the day. All the patients were given the diet prepared for patients in the wards, containing 2 Gm. of salt. The intake of fluid was fixed. The methods and order of making observations were recorded in our first paper.[3] In the technic of rebreathing for estimation of the arteriovenous oxygen difference, the amount of gas in the "rebreathing bag" was adjusted to the amount which, as had been found by trial beforehand, the patient could take completely.

Observations.—Observations were made on 11 patients. In 6 of these cases the etiologic diagnosis was hypertension (cases 1 to 6, inclusive), in 2 rheumatic fever (cases 7 and 8), in 1 syphilis (case 9), in 1 arteriosclerosis (case 10) and in 1 tuberculosis, giving rise to chronic constrictive pericarditis (case 11). All the patients exhibited signs and symptoms of congestive heart failure.

The case of A. F. (case 1) illustrates the effect of giving digatilis in the presence of congestive heart failure as a consequence of hypertension. During failure the cardiac output was diminished, the heart large, the circulation time prolonged and the venous pressure elevated (table 1). The patient was so ill that treatment with digitalis was started immediately after these observations were recorded, and digitalization was continued into the following day; he received the digitalizing amount, 1.8 Gm. in twenty-four hours, and the maintenance amount for the second day. The administration of 2.1 Gm. of digitalis in thirty-six hours resulted in an increase in the cardiac output per minute (table 1 and fig. 1) and per beat, a decrease in the cardiac size, a shortening of the circulation time, a lowering of the venous pressure and an increase in

4. See the tables for exceptions.

vital capacity. With the continued use of digitalis these relations were maintained, the heart, however, becoming still smaller. The patient's condition improved, and he became free from the signs and symptoms of heart failure.

The data for a second patient (E. R.) in this group (case 4, table 1) illustrate the effect of the drug in the presence of paroxysmal nocturnal dyspnea. The patient was being given 3 Gm. of theobromine with sodium salicylate daily, and this was kept constant during the period of the observations. The giving of 1.8 Gm. of digitalis to this patient resulted in twenty-four hours in an increase in cardiac output (fig. 2), a decrease in cardiac size (figs. 2 and 3), a shortening of the circulation time and no significant change in the venous pressure, which was not elevated. The patient began sleeping better at once.

The data for S. S. (case 7) illustrate the effect of giving digitalis in the presence of rheumatic heart disease (table 1). After 1.7 Gm. of the drug was given, the cardiac output increased (table 1 and fig. 4), the cardiac size decreased (figs. 4 and 5), the circulation time decreased and the venous pressure fell. The patient became free from the signs and symptoms of congestive heart failure.

The data for J. K. (case 9) illustrate the effect of giving digitalis in the presence of syphilitic heart disease (table 1). The administration of 1.8 Gm. of the drug in twenty-four hours resulted in an increase in cardiac output, a decrease in cardiac size, a shortening of the circulation time and a fall in the venous pressure (fig. 6).

The case of C. K. (case 10) illustrates the effect of giving digitalis in the presence of arteriosclerotic heart disease (table 1). The patient was under the influence of digitalis when the first observations were made, on Oct. 25, 1935 (fig. 7). The use of digitalis was discontinued, and in the next sixteen days signs of congestive heart failure recurred and the patient gained weight. At this time, on November 13, the heart had dilated from 155.3 to 176.2 sq. cm., the cardiac output had decreased from 3.13 to 2.38 liters per minute, the circulation time had increased from twenty-two and seven tenths to thirty seconds and the venous pressure had risen from 9.4 to 19 cm. On November 14, 1.8 Gm. of digitalis was given. On November 15 the cardiac output had increased to 2.8 liters per minute, the size of the heart had decreased to 164.3 sq. cm., the circulation time had fallen to twenty and eight-tenths seconds and the venous pressure had fallen to 11.4 cm. There were diuresis and a loss of weight.

The effect of the drug after the resection of part of the pericardium of a patient suffering from chronic constrictive pericarditis is shown in case 11 (table 1). This patient, also, showed an increase in cardiac output and a fall in venous pressure. The cardiac area was not measured, because of the presence of fluid in the right pleural cavity.

TABLE 1.—*Data Relating to the Effect of Digitalis in Eleven Cases*

Case	Age	Sex	Date	Body Surface, Sq.M.	Oxygen Consumption, Cc. per Min.	Arteriovenous Oxygen Difference, Cc.	Cardiac Output, L. per Min.	Cardiac Output, L. per Sq.M. per Min.	Cardiac Area, Sq.Cm.	Cardiac Volume, Cc.*	Arterial Pressure, Mm. Hg	Circulation Time, Sec.
Hypertensive Heart Disease												
1	38	M	1/ 4/36	1.62	286	110.9	2.58	1.59	167.2	1,970	211/145	22.3
A. F.			1/4-5 36	....	...	.....	....	....	.....	.....	.....	....
			1/ 6/36	1.57	249	66.6	3.74	2.38	147.6	1,634	204/108	15.3
			1/ 8/36	1.54	205	68.9	3.00	1.95	137.3	1,466	192/132	16.4
			1/15/36	1.55	203	59.6	3.41	2.20	128.3	1,326	205/128	12.5
2	68	M	1/21/36	1.83	274	117.6	2.33	1.27	172.3	2,059	170/ 94	25.9
M. R.			1/22/36	....	...	.....	....	....	.....	.....	.....	....
			1/23/36	1.82	273	83.0	3.29	1.80	157.9	1,805	174/108	21.4
			1/29/36	1.79	207	68.0	3.04	1.70	150.8	1,685	170/ 80	19.2
3	53	M	11/23/35	1.71	280	98.3	2.85	1.66	218.2	2,935	153/110	35.1
M. H.			11/24/35	....	...	.....	....	....	.....	.....	.....	....
			11/25/35	1.70	241	79.7	3.03	1.80	196.8	2,515	162/110	36.1
			11/27/35	1.70	216	71.9	3.00	1.80	197.7	2,532	160/102	30.6
			12/ 3/35	1.68	230	68.9	3.34	2.00	196.0	2,500	148/ 98	29.1
			12/11/35	1.69	220	70.9	3.10	1.84	196.7	2,512	148/ 95	29.0
4	44	M	5/11/35	1.78	265	77.9	3.40	1.91	212.3	2,822	150/108	30.0
E. R.			5/12/35	....	...	.....	....	....	.....	.....	.....	....
			5/13/35	1.77	251	66.6	3.80	2.15	184.2	2,280	166/110	23.0
			5/15/35	1.77	232	65.3	3.60	2.00	178.4	2,172	158/110	26.2
5	51	M	3/ 5/36	2.00	263	81.4	3.23	1.62	234.2	3,263	160/110	50.0
F. G.			3/ 6/36	....	...	.....	....	....	.....	.....	.....	....
			3/ 7/36	1.99	263	72.8	3.61	1.82	215.0	2,875	190/ 94	42.0
			3/ 9/36	1.94	265	73.4	3.61	1.86	207.1	2,717	160/108	46.4
6	64	M	2/29/36	1.77	249	82.8	3.01	1.70	141.1	1,526	200/114	15.8
L. B.			2/29-3/ 1/36	....	...	.....	....	....	.....	.....	.....	....
			3/ 2/36	1.76	218	63.7	3.42	1.94	133.6	1,435	212/108	16.0
			3/ 6/36	1.73	216	59.2	3.65	2.11	125.9	1,287	212/100	16.4
Rheumatic Heart Disease												
7	32	M	2/19/36	1.73	245	115.8	2.13	1.23	215.6	2,882	114/ 76	42.6
S. S.			2/20/36	....	...	.....	....	....	.....	.....	.....	....
			2/22/36	1.71	238	78.1	3.05	1.80	193.0	2,441	115/ 64	31.4
			2/24/36	1.68	236	74.3	3.20	1.90	172.9	2,070	105/ 58	31.7
8	32	F	4/28/36	1.48	207	106.3	1.95	1.32	194.2	2,448	110/ 80	27.0
W. B.			4/29/36	....	...	.....	....	....	.....	.....	.....	....
			4/30/36	1.48	201	85.2	2.36	1.59	170.0	2,020	122/ 80	23.4
			5/ 2/36	1.46	205	84.0	2.44	1.67	175.4	2,118	116/ 72	27.0
			5/ 7/36	1.39	166	82.3	2.02	1.50	183.4	2,260	98/ 65	24.0
Syphilitic Heart Disease												
9	55	M	4/15/36	1.65	220	107.5	2.05	1.26	204.5	2,680	156/ 40	25.8
J. K.			4/16/36	....	...	.....	....	....	.....	.....	.....	....
			4/17/36	1.64	220	80.9	2.72	1.66	175.9	2,107	156/ 40	22.0
Arteriosclerotic Heart Disease												
10	48	M	10/25/35	1.55	218	69.6	3.13	2.02	155.3	1,772	106/ 74	22.7
C. K.			11/13/35	1.59	212	88.9	2.38	1.50	176.2	2,133	97/ 78	30.0
			11/14/35	....	...	.....	....	....	.....	.....	.....	....
			11/15/35	1.58	212	74.4	2.85	1.80	164.3	1,905	116/ 50	29.8
			11/18/35	1.57	207	72.8	2.84	1.81	160.4	1,833	106/ 58	30.4
			11/21/35	1.53	209	73.9	2.83	1.85	172.1	2,000	104/ 80	28.0
Chronic Constrictive Pericarditis after Pericardial Resection (Jan. 28, 1936)												
11	30	F	2/13/36	1.44	186	85.0	2.19	1.52	.....	.....	100/ 75	10.9
A. R.			2/14/36	....	...	.....	....	....	.....	.....	.....	....
			2/15/36	1.42	184	66.7	2.76	1.94	Could not be measured		96/ 64	10.2
			2/18/36	1.44	184	73.5	2.65	1.84	(fluid in chest)		105/ 75	9.9

* The volumes have not been multiplied by the constant included in Bardeen's formula, as stated in text.

† + and 0 indicate, in this table as well as in table 2, that diuresis did or did not take place.

§ In this table, as well as in table 2, Hypt. indicates hypertension; Enl. Ht., enlarged heart; Artscl., arteriosclerosis; R-I-V-HB, right intraventricular heart block; Rheu. fever, rheumatic fever; M.S., M.I. and A.I., mitral stenosis, mitral insufficiency and aortic insufficiency, respectively; Tbc., tuberculosis. The diagnoses in this paper conform to those recommended by the New York Tuberculosis and Health Association.

§ In this table as well as in table 2, 0 indicates not present; +, present; ↓, decreasing; ↑, increasing; ±, doubtful.

Circulation Time, Sec.	Venous Pressure, Cm.	Vital Capacity, Cc.	Cardiac Rate, per Min.	Cardiac Output, Cc. per Beat	Work of Left Ventricle, Gm. M. per Beat	Digitalis, Gm.	Diuresis†	Diagnosis‡	Signs of Failure§						Red Blood Cell Count and Hemoglobin Value††
									Cyanosis	Liver	Rales	Edema	Dyspnea	Fluid in Chest	
Hypertensive Heart Disease															
22.3	21.0	1,400	94	29	76	...	+	Hypt.;	0	+	+	0	+	0	3.9
....	.....	.....	..	..	..	2.1		Enl. Ht.							82
15.3	6.6	1,900	76	49	94	0.2 q.d.¶			0	↓	0	0	0	0	
16.4	7.8	2,100	76	40	88	0.2 q.d.			0	?	0	0	0	0	
12.5	8.5	2,450	70	49	111	0.2 q.d.			0	±	0	0	0	0	
25.9	21.3	1,600	120	20	36	...	0	Artscl.;	±	+	+	+	+	0	4.1
....	.....	.....	..	..	..	1.5#		Enl. Ht.;							92
21.4	13.8	2,300	94	35	67			Hypt.	±	±	↓	0	±	0	
19.2	7.9	2,800	60	50	85	0.1 q.d.			0	0	0	0	0	0	
35.1	10.7	1,900	82	35	63	...	Slight	Artscl.;	+	+	+	0	+	+	4.0
....	.....	.....	..	..	..	1.8		Hypt.;							94
26.1	7.2	2,300	64	47	87	0.2 q.d.		Enl. Ht.;	↓	↓	↓	0	0	↓	
36.6	7.6	2,600	68	44	78	0.2 q.d.		R-I-V-HB	0	?	±	0	0	±	
29.1	6.4	2,850	64	52	87	0.2 q.d.			0	↓	0	0	0	0	
29.0	7.0	2,950	60	52	86	0.2 q.d.			0	?	0	0	0	0	
30.0	8.4	3,400	98	35	61	...	0 ?	Hypt.;	+	0	+	0	+	0	4.9
....	.....	.....	..	..	..	1.8#		Enl. Ht.							90
23.0	6.9	3,750	80	48	90	0.2 on			0	0	0	0	0	0	
26.2	7.9	3,900	80	45	82	May 14			0	0	0	0	0	0	
50.0	21.5	2,700	68	47	86	...	+	Hypt.;	+	+	+	+	+	0	5.7
....	.....	.....	..	..	..	1.8		Enl. Ht.							104
42.0	12.3	2,800	66	55	106				↓	↓	↓	↓	↓	0	
40.4	13.3	2,900	58	62	113				?	↓	±	0	±	0	
15.8	18.6	1,300	100	30	66	...	Lost	Artscl.;	+	+	+	±	+	0	4.5
....	.....	.....	..	..	..	2.2	weight	Hypt.;							80
16.6	4.3	1,800	74	46	100	0.2 q.d.		Enl. Ht.	↓	±	+	±	↓	0	
16.4	5.0	1,900	66	55	116	0.2 q.d.			0	0	+	0	±	0	
Rheumatic Heart Disease															
42.6	18.1	3,200	70	30	39	...	+	Rheu. fever;	+	+	+	0	0	0	4.9
....	.....	.....	..	..	..	1.7		M.S.;							100
31.4	9.7	3,400	54	56	69	0.2 q.d.		M.I.;	0	↓	0	0	0	0	
31.7	5.8	3,450	58	55	61	0.2 q.d.		Enl. Ht.	0	?	0	0	0	0	
27.0	17.0	1,500	80	24	31	...	Lost	Rheu. fever;	+	+	+	+	+	±	108
....	.....	.....	..	..	..	1.8	weight	M.S.;							
23.4	11.0	1,500	80	30	41	0.2 q.d.		M.I.;	↓	↓	↓	↓	↓	±	
27.0	11.2	1,500	72	34	46	0.2 q.d.		Enl. Ht.	0	?	↓	↓	0	0	
24.0	3.3	2,100	48	42	47	0.2 q.d.			0	0	0	0	0	0	
Syphilitic Heart Disease															
25.8	18.3	1,500	98	21	28	...	Slight	Syphilis	+	+	+	+	+	+	4.9
....	.....	.....	..	..	..	1.8		A.I.;							
22.6	10.5	1,100	116	23	31			Enl. Ht.	±	+	+	+	↓	↓	
Arteriosclerotic Heart Disease															
22.7	9.4	2,900	112	28	34	+**	+	Artscl.;	±	+	0	0	0	0	4.5
30.0	19.6	2,300	114	21	25			Enl. Ht.	+	↑	0	+	+	0	74
....	.....	.....	..	..	..	1.8									
20.8	11.4	2,250	100	29	34				0	0	0	0	0	0	
30.4	8.7	2,800	100	28	32	0.2 q.d.			0	±	0	0	0	0	
28.0	9.4	3,050	96	30	37				0	±	0	0	0	0	
Chronic Constrictive Pericarditis after Pericardial Resection (Jan. 28, 1936)															
10.9	27.8	1,000	110	20	24	...	+	Tbc.; chronic	±	+	+	0	0	±	3.9
....	.....	.....	..	..	..	1.8		constrictive							77
10.2	22.7	900	96	29	32			pericarditis	0	+	+	0	0	±	
9.9	22.0	950	84	32	39	0.2 q.d.			±	+	+	0	0	±	

†† The values for red blood cells are given in millions; those for hemoglobin are given in percentages, 14.5 Gm. of hemoglobin being equivalent to 100 per cent.

¶ When the patient was kept under the influence of digitalis, the measurements were made as usual in the morning, and the maintenance dose of digitalis was given later in the day.

This patient received 1 Gm. of theobromine with sodium salicylate three times a day, from April 23, 1935. The dosage was not changed during the period of these observations.

** This patient received 1.5 Gm. of a mixture of calcium theobromine and calcium salicylate three times a day. The dosage was continued unchanged throughout the period of these observations. The patient was under the influence of digitalis at this time, but its use was discontinued after the observations were made.

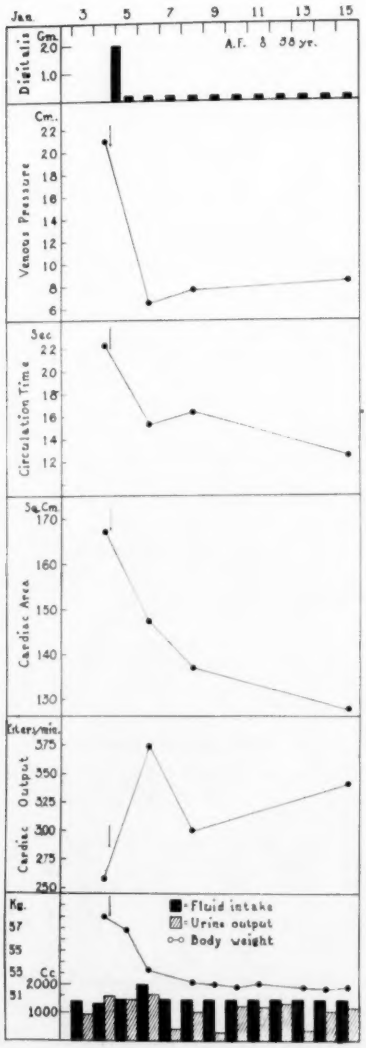
Jan. 3 5 7 9 11 13 15
Digitalis Gm. 2.0 1.0
A.F. ♂ 58 yr.
Venous Pressure Cm. 22 20 18 16 14 12 10 8 6
Circulation Time Sec. 22 20 18 16 14 12
Cardiac Area Sq.Cm. 170 160 150 140 130
Cardiac Output Liters/min. 375 350 325 300 275 250
Kg. 57 55 53 51
Cc 2000 1000
Fluid intake
Urine output
Body weight

Fig. 1.—The effect of digitalis on urinary output and body weight, cardiac output, cardiac size, circulation time and venous pressure in case 1 in the presence of hypertensive heart disease. This patient, as well as those whose data are given in figures 2 to 7, inclusive, showed a normal sinus rhythm.

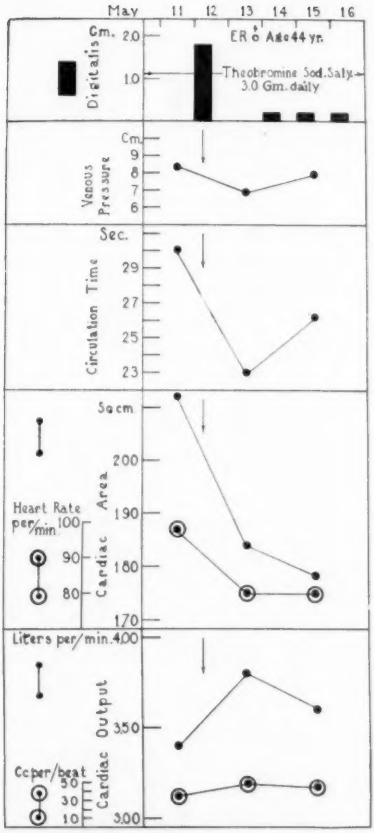

Fig. 2.—The effect of digitalis on the cardiac output per beat and per minute, heart rate, cardiac size, circulation time and venous pressure in case 4 (hypertensive heart disease) at a time when the predominant symptom was paroxysmal nocturnal dyspnea.

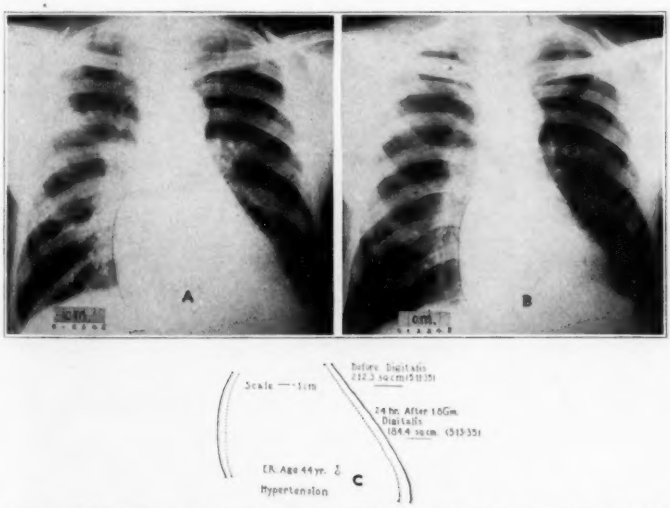

Fig. 3.—The change in the size of the heart after the administration of 1.8 Gm. of digitalis in case 4. *A* was taken (May 11, 1935) before and *B* was taken (May 13) twenty-four hours after the administration of the drug. In *C* are shown superimposed the outlines of the heart obtained from tracings of *A* and *B*.

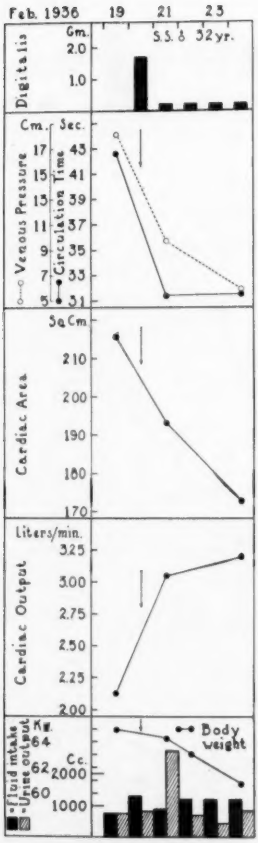

Fig. 4.—The effect of digitalis on the urinary output and body weight, cardiac output, cardiac size, venous pressure and circulation time in case 7 (rheumatic heart disease).

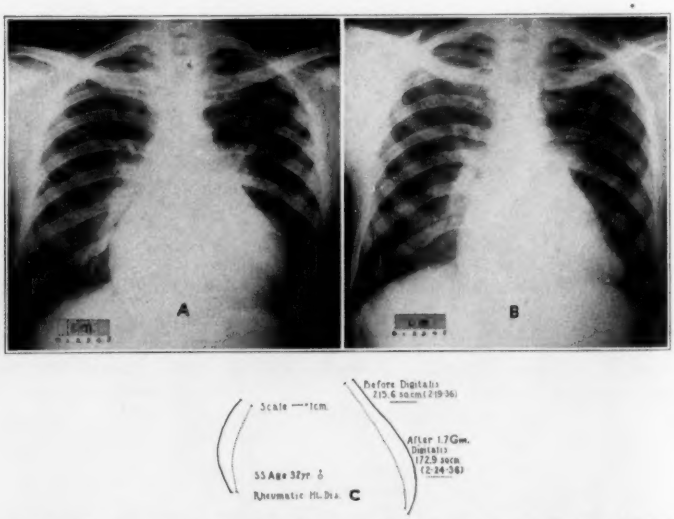

Fig. 5.—The change in the size of the heart after the administration of 1.7 Gm. of digitalis in case 7. *A* was taken (Feb. 19, 1936) before and *B* (February 24) three days after the administration of the drug. In *C* are shown superimposed the outlines of the heart obtained from tracings of *A* and *B*.

II. OBSERVATIONS ON PATIENTS EXHIBITING AURICULAR FIBRILLATION

Plan of Observations.—Observations were made on 9 patients with auricular fibrillation. In 7 cases the etiologic factor was rheumatic fever,

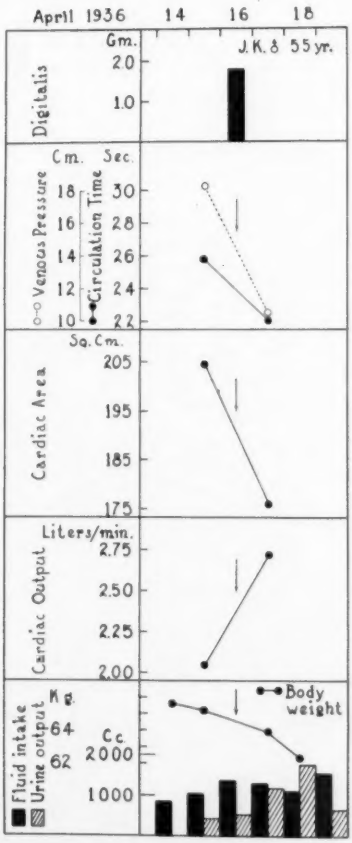

Fig. 6.—The effect of digitalis on urinary output and body weight, cardiac output, cardiac size, venous pressure and circulation time in case 9 (syphilitic heart disease).

in 1 syphilis and in 1 arteriosclerosis. In all there was evidence of congestive heart failure. The amount of the drug and the plan of procedure were similar to those followed in the cases of normal sinus rhythm.

Observations.—The results secured in the case of J. G. (case 12) serve to illustrate the course of events in a patient with elevation of the

venous pressure (cases 12, 15, 19 and 20, table 2). Giving digitalis to this patient (1.8 Gm. in twenty-four hours) resulted within twenty-four hours in an increase in cardiac output, a decrease in cardiac size

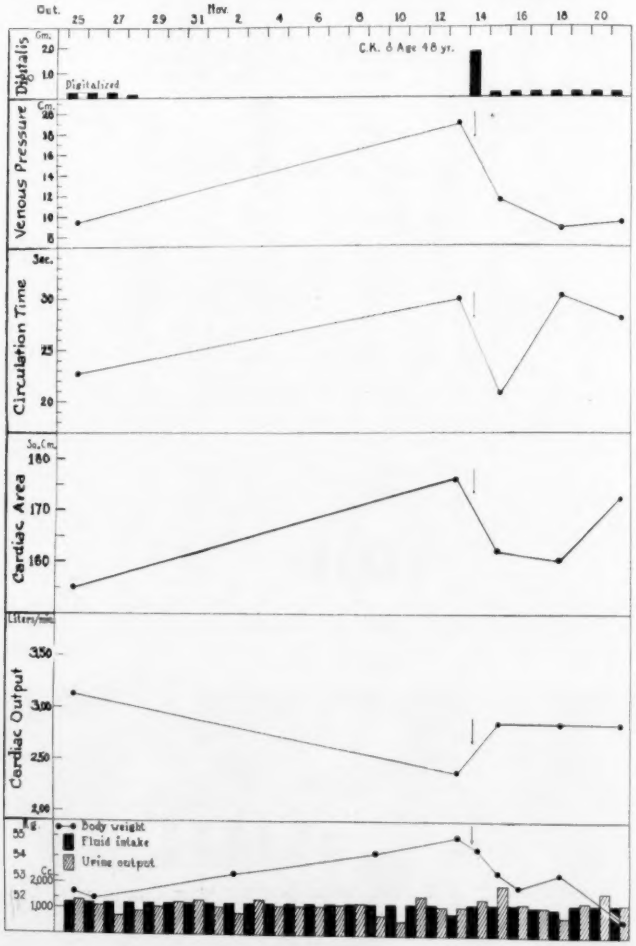

Fig. 7.—The effect of digitalis on urinary output and body weight, cardiac output, cardiac size, circulation time and venous pressure in case 10 (arteriosclerotic heart disease).

(fig. 8), a shortening of circulation time and a fall in venous pressure. There was a fall in ventricular rate from 102 to 52 per minute, and the

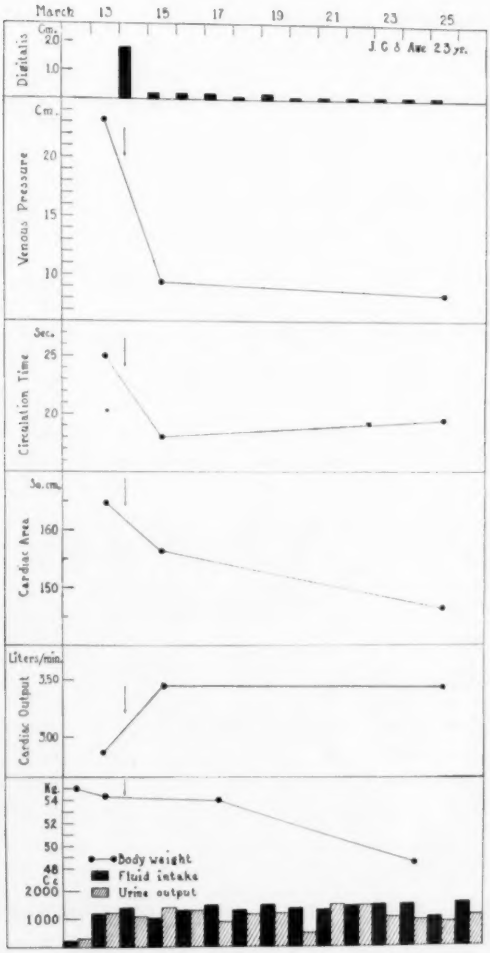

Fig. 8.—The effect of digitalis on urinary output and body weight, cardiac output, cardiac size, circulation time and venous pressure in case 12 (rheumatic heart disease). In this patient as well as in those whose data are given in figures 10 to 12, auricular fibrillation was present.

output per beat was more than doubled (table 2). The signs of heart failure became less. Ten days later (March 25), the use of the drug being continued, the cardiac output, circulation time and venous pressure remained unchanged, but the cardiac size was still smaller.

TABLE 2.—*Data Relating to Nine Patients With Co*

Case	Age	Sex	Date	Body Surface, Sq.M.	Oxygen Consumption, Cc. per Min.	Arteriovenous Oxygen Difference, Cc.	Cardiac Output, L. per Min.	Cardiac Output, L. per Sq.M. per Min.	Cardiac Area, Sq.Cm.	Cardiac Volume, Cc.*	Arterial Pressure, Mm. Hg	Circulation Time, Sec.
12 J. G.	28	M	3/13/35	1.57	272	95.2	2.86	1.82	164.3	1,920	150-130/ 90	25.4
			3/14/35	....	...	.....	....	....	.....	.....	.....	...
			3/15/35	1.54	267	79.4	3.36	2.18	156.2	1,780	126/ 60	18.0
			3/25/35	1.50	247	74.1	3.33	2.22	146.5	1,615	134/ 65	19.5
13 A. C.	32	M	3/27/35	1.80	278	119.8	2.32	1.28	171.9	2,057	94/ 56	28.0
			3/28/35	....	...	.....	....	....	.....	.....	.....	...
			3/30/35	1.79	269	84.6	3.20	1.78	163.8	1,910	94/ 52	20.0
			4/ 2/35	1.80	263	78.3	3.36	1.86	154.9	1,757	114/ 76	18.0
14 L. C.	30	F	3/ 4/35	1.66	222	96.8	2.29	1.38	202.9	2,640	120-110/ 74	22.5
			3/ 5/35	....	...	.....	....	....	.....	.....	.....	...
			3/ 6/35	1.66	207	74.4	2.78	1.70	185.3	2,298	118-110/ 74	20.2
15 M. C.	53	F	1/28/36	1.61	207	102.9	2.01	1.25	194.2	2,490	170/100	34.0
			1/29/36	....	...	.....	....	....	.....	.....	.....	...
			1/30/36	1.61	201	89.3	2.25	1.40	179.3	2,188	170-162/100	15.8
			2/ 1/36	1.60	197	87.6	2.25	1.40	170.1	2,021	188/105	16.1
			2/14/36	1.60	193	77.8	2.48	1.55	168.7	2,000	150/ 70	22.2
16 G. MacF.	57	M	2/25/36	1.52	189	84.2	2.24	1.47	158.6	1,821	110/ 90	24.0
			2/26/36	....	...	.....	....	....	.....	.....	.....	...
			2/27/36	1.52	193	84.6	2.28	1.50	153.8	1,740	120/ 74	22.6
			2/29/36	1.51	182	70.8	2.57	1.70	143.1	1,560	118/ 62	19.7
17 J. M.	37	M	2/27/34	1.72	203	100.5	2.02	1.17	218.0	2,932	140/ 80	....
			3/1-3/ 3/34	....	...	.....	....	....	.....	.....	.....	...
			3/ 4/34	1.72	221	95.6	2.31	1.34	205.4	2,682	140/ 80††	...
18 M. P.	41	F	4/30/34	1.54	180	90.6	1.98	1.28	173.2	2,079	112/ 70	....
			5/ 1/34	....	...	.....	....	....	.....	.....	.....	...
			5/ 2/34	1.54	172	90.6	1.90	1.23	167.3	1,975	105/ 80	....
			5/ 5/34	1.52	164	79.9	2.05	1.35	157.2	1,798	105/ 80	....
			5/10/34	1.53	159	74.3	2.14	1.40	162.0	1,881	100/ 70	....
19 F. K.	61	M	2/28/35	1.99	240	83.1	2.89	1.45	198.0	2,540	174-160/110	20.1
			3/ 1/35	....	...	.....	....	....	.....	.....	.....	...
			3/ 2/35	1.97	240	74.4	3.23	1.64	169.1	2,005	140-130/ 76	17.9
20 F. St. J.	73	M	9/25/35	1.89	245	94.4	2.60	1.37	166.6	1,960	150/ 90	35.0
			9/26/35	....	...	.....	....	....	.....	.....	.....	...
			9/27/35	1.84	247	77.4	3.19	1.73	156.3	1,779	150-140/ 68	22.5
			10/ 2/35	1.77	241	81.2	3.00	1.70	157.1	1,794	136-130/ 80	33.0

* The volumes have not been multiplied by the constant included in Bardeen's formula, as stated in text.

† Apical rate.

†† The blood pressure was not taken on these days; the figures obtained on February 27 were used for calculations.

The results in the case of A. C. (case 13) serve to illustrate the course of events in a patient without elevation of the venous pressure (cases 13, 14 and 16). Giving digitalis (1.8 Gm.) resulted in an increase in cardiac output per minute and per beat (table 2 and fig. 9), a decrease in cardiac size (fig. 10), a shortening of circulation time and no significant change in venous pressure. There was relief from the signs and symptoms of congestive heart failure.

WORK OF THE HEART

The effect of digitalis on the work of the left ventricle per beat was estimated, as it was for the paper relating to compensated heart disease.[3] Starr and his associates [5] have found that the work of the left ventricle

gestive Heart Failure Exhibiting Auricular Fibrillation

Venous Pressure, Cm.	Vital Capacity, Cc.	Cardiac Rate, per Min.†	Cardiac Output, Cc. per Beat	Work of Left Ventricle, Gm. M. per Beat	Digitalis, Gm.	Diuresis	Diagnosis‡	Signs of Failure: Cyanosis	Liver	Rales	Edema	Dyspnea	Fluid in Chest	Red Blood Cell Count and Hemoglobin Value§
22.2	2,600	102	28	43.8	...	+	M.S.;	+	+	+	+	+	0	5.7
....	.....	..	..	....	1.8		M.I.;							115
9.3	2,900	52	66	84.7	0.2 q.d.		Enl. Ht.;	0	±	0	0	0	0	
8.1	3,250	60	56	76.2			IIB	0	0	0	0	0	0	
7.2	3,500	150	15	15.3	...	Lost weight	M.S.; M.I.;	+	+	+	0	+	0	4.5
....	.....	..	..	....	1.8		A.I.;							95
7.5	4,000	102	32	33.4	0.2 (March 29) q.d.		Enl. Ht.;	0	0	0	0	0	0	
4.7	4,350	72	47	60.7			IIB	0	0	0	0	0	0	
6.6	2,750	100	23	31.3	...	Slight	M.S.; M.I.;	+	+	0	+	+	0	6.0
....	.....	..	..	....	1.7		Enl. Ht.;							107
6.4	2,700	70	40	58.9			IIB	0	±	0	0	0	0	
11.4	1,550	100	20	36.7	...	0	M.S.; M.I.;	+	+	+	+	0	+	5.1
....	.....	..	..	....	1.8		Hypt.;							95
6.0	2,000	68	33	37.4	0.2 q.d.		Enl. Ht.;	+	±	0	±	0	±	
5.8	1,900	72	31	62.0			IIB	0	0	0	0	0	0	
8.1	2,000	70	35	52.3				0	0	0	0	0	0	
7.9	1,750	84	27	36.7	...	+	M.S.; M.I.;	+	+	+	0	0	0	4.6
....	.....	..	..	....	1.8		Enl. Ht.;							90
4.6	1,900	78	29	38.3	0.2 q.d.		IIB	0	0	±	0	0	0	
2.9	1,850	68	38	46.5				0	0	±	0	0	0	
....	2,700	76	27	40.4	1.0 (3/1)	0	M.S.; M.I.;	+	+	+	0	+	0	3.8
....	.....	..	..	....	1.2 (3/2)		Enl. Ht.;							92
....	2,075	75	31	46.4	0.2 (3/3)		IIB	↓	↓	0	0	↓	0	
...	2,080	124	16	19.8	...	0	M.S.; M.I.;	0	+	+	0	0	0	5.1
....	.....	..	..	....	1.8		Enl. Ht.;							84
....	2,090	86	22	27.8	0.2 q.d.		IIB	0	+	+	0	0	0	
.....	2,200	71	30	37.9				0	↓	↓	0	0	0	
....	2,200	59	36	41.6				0	↓	↓.	0	0	0	
....														
17.2	2,200	119	24	44.6	...	Lost weight	Aneurysm;	+	0	+	+	+	0	5.2
....	.....	..	..	....	2.0		Enl. Ht.;							100
12.1	2,750	90	36	52.0			IIB	+	0	+	↓	↓	0	
14.8	1,200	60	43	70.2	...	+	Artscl.;	+	+	+	+	+	0	4.4
....	.....	..	..	....	1.5¶		Enl. Ht.;							86
9.3	1,600	58	55	80.0			IIB	↓	↓	↓	↓	↓	0	
8.0	1,800	66	45	65.5				±	±	±	±	↓	0	

‡ IIA indicates the classification number.
¶ This patient received 1.5 Gm. of theocalcin three times a day throughout the period of these observations.
§ The values for red blood cells are given in millions; those for hemoglobin are given in percentages, 14.5 Gm. of hemoglobin being equivalent to 100 per cent.

5. (*a*) Starr, I., Jr.; Collins, L. H., and Wood, F. C.: Studies of the Basal Work and Output of the Heart in Clinical Conditions, J. Clin. Investigation **12**:13 (Jan.) 1933. (*b*) Starr, I., Jr.; Donal, J. S.; Margolies, A.; Shaw, R.; Collins, L. H., and Gamble, C. J.: Studies of the Heart and Circulation in Disease: Estimations of Basal Cardiac Output, Metabolism, Heart Size, and Blood Pressure in Two Hundred and Thirty-Five Subjects, ibid. **13**:561 (July) 1934.

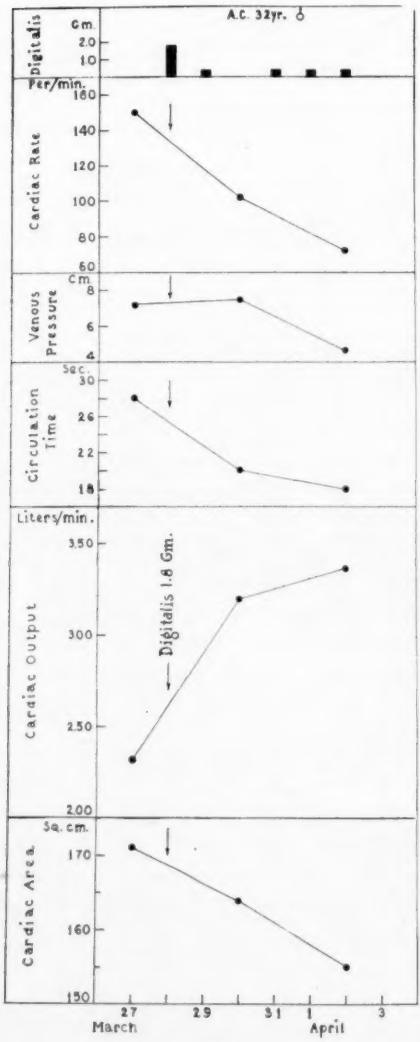

Fig. 9.—The effect of digitalis on cardiac size, cardiac output, circulation time, venous pressure and ventricular rate in case 13 (rheumatic heart disease). The venous pressure was not elevated during congestive failure in this instance.

which is maintaining an adequate circulation bears a linear relation to the size of the heart. From their data they have defined a zone of normal circulatory function. In a manner similar to theirs, we have plotted cardiac volumes as abscissas and gram meters of work of the left ventricle per beat as ordinates (tables 1 and 2 and figs. 11 and 12). During failure the values for all the patients except 1 (case 6, normal sinus rhythm) fell below line *CD*, outside the zone of normal circulatory function, whether the rhythm was regular (fig. 11) or that of auricular fibrillation (fig. 12). When digitalis was given, however, all the values

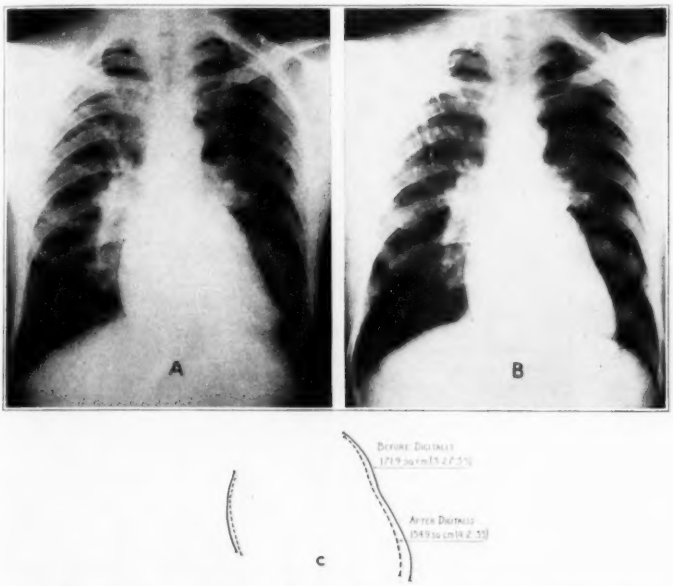

Fig. 10.—The change in the size of the heart after the administration of 1.8 Gm. of digitalis in case 13. *A* was taken (March 27, 1935) before and *B* (April 2) three days after the administration of the drug. In *C* are shown superimposed the outlines of the heart obtained from tracings of *A* and *B*.

moved closer to or into the zone of normal circulatory function. In short, the work of the left ventricle per beat became more nearly commensurate with what was expected of the heart for its size.

SUMMARY

The cardiac output was decreased, and the heart size was increased in 20 cases of heart failure of the congestive type. The administration of digitalis to 11 of these patients in whom the rhythm was regular and

to 9 with auricular fibrillation resulted in twenty-four hours in an increase in cardiac output, a decrease in cardiac size, a shortening of circulation time, and a fall in venous pressure if it was elevated.

Moreover, giving digitalis to these patients increased the work of the heart per beat; a decrease in the size of the heart also having

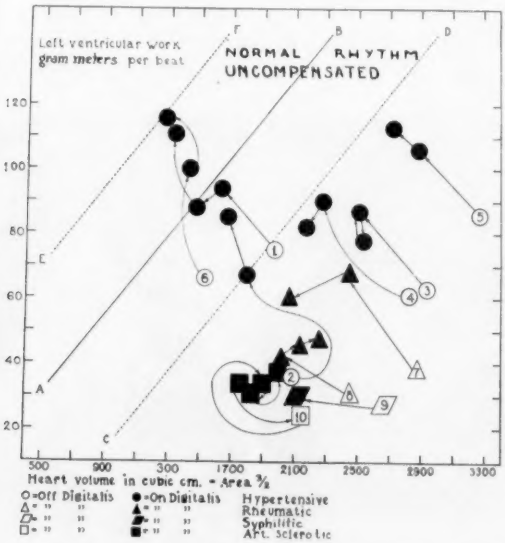

Fig. 11.—Data relating to the work of the left ventricle per beat and the cardiac volume in cases of congestive heart failure when normal sinus rhythm was present. Data relating to the work of the left ventricle per beat (cases 1 to 10 inclusive, table 1) are plotted against the corresponding cardiac volumes. Line *AB* represents the best line, the regression of the work on the volume, defined by Starr, Collins and Wood [5a] on the basis of a statistical treatment of data for a control group of cases. Lines *CD* and *EF* were placed by these authors at a distance of twice the standard deviation from *AB*. It appears from their observations that a patient whose values fall within zone *CD-EF* has a normal circulatory function; that is to say, the work of the heart is commensurate with its size; on the other hand, they found that the values relating to patients who had suffered from cardiac decompensation fell in a zone below *CD*. The values for all the patients represented in this figure except L. B. (case 6) fell in the zone below *CD* before digitalis was given, that is to say, in the zone indicative of heart failure. The cause of the heart disease in each case is indicated by the shape of the symbol employed, in accordance with the key shown at the bottom of the figure. Open symbols represent the position of the values before digitalis was given and closed symbols their position after the exhibition of the drug. Arrows indicate the changes in position which occurred after digitalization. It will be observed that in all instances digitalis made the values take up a more advantageous position on the chart, closer to or into the zone of normal circulatory function. This change was particularly marked in cases 1 and 2, the values passing above line *CD*, into the zone of normal circulatory function.

occurred, the work per beat became more nearly commensurate with its size (figs. 11 and 12), and the value for the patients moved closer to or into the zone of normal circulatory function.

COMMENT

On the basis of our former studies of the action of digitalis [6] as well as our present observations, we have been able to demonstrate clinically

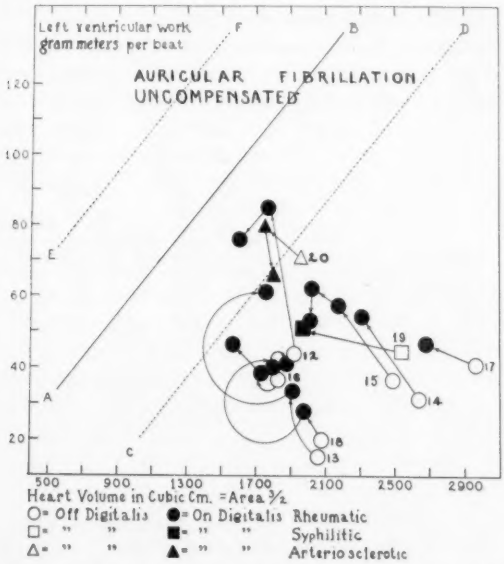

Fig. 12.—Data relating to the work of the left ventricle per beat and the cardiac volume in cases of congestive heart failure with auricular fibrillation (cases 12 to 20, inclusive, table 2). This chart is made in the same fashion as figure 8. The interpretation of the symbols is identical with that given in figure 8. All the values fell below line *CD*, outside the zone of normal circulatory function. After the exhibition of digitalis, the values in all 9 cases moved closer to *CD* or even up into zone *CD-EF* and consequently assumed a more advantageous position on the chart. This change was of particular interest in cases 12 and 20, the values passing above line *CD*, into the zone of normal circulatory function.

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6. (*a*) Cohn, A. E., and Stewart, H. J.: Evidence That Digitalis Influences Contraction of the Heart in Man, J. Clin. Investigation **1**:97 (Oct.) 1924; (*b*) The Relation Between Cardiac Size and Cardiac Output per Minute Following the Administration of Digitalis in Normal Dogs, ibid. **6**:53 (Aug.) 1928; (*c*) The Relation Between Cardiac Size and Cardiac Output per Minute Following The Administration of Digitalis in Dogs in Which the Heart Is Enlarged, ibid.

(Footnote continued on next page)

certain consequences of giving the drug which may be summarized to present our point of view (table 3). It appears that:

1. Digitalis increases the extent of ventricular contraction in man and in dogs.[6a-c]

2. Digitalis decreases the cardiac output [1] and the cardiac size [1] of normal persons without decreasing the venous pressure.[1]

3. When digitalis is given to patients suffering from organic heart disease who exhibit regular sinus rhythm without congestive heart failure, it may: (*a*) decrease the size, decrease the output and increase the circulation time, (*b*) decrease the size, increase the cardiac output and decrease the circulation time or (*c*) leave the size, cardiac output and circulation time all unchanged. The venous pressure was not sig-

TABLE 3.—*Actions of Digitalis That May Be Observed Clinically* *

Clinical State	Species	Rhythm†	Changes in T Wave	Heart Rate	Extent of Ventricular Contraction	Cardiac Size	Cardiac Output	Work per Beat	Circulation Time	Venous Pressure
Normal.....	Dog	N.R.	Yes	—	+	—	—	?	?	?
	Man	N.R.	Yes	—	+	—	—	+	?	0
Organic heart disease Without failure	Dog	N.R.	Yes	—	+	—	—	?	?	?
	Man	N.R.	Yes	—	+	—	—	+	+	0
			Yes	—	+	0	0	+	0	0
			Yes	—	+	—	+	+	—	0
		A.F.	Yes	—	+	0	0	+	0	0
			Yes	—	+	—	+	+	—	0
	Dog	A.F.	Yes	—	?	—	+	?	?	?
With failure...	Man	A.F.	Yes	—	+	—	+	+	—	—
		N.R.	Yes	—	+	—	+	+	—	—
	Dog	N.R.	Yes	—	+	—	+	?	?	?

* In this table — indicates decrease +, increase; 0, no change ?, not known.
† N.R. indicates normal sinus rhythm; A.F., auricular fibrillation.

nificantly altered.[3] In short, in some cases the heart behaved like a failing heart and in others like a normal one.

4. In cases of auricular fibrillation without congestive heart failure, digitalis may increase the cardiac output and decrease the size and circulation time or leave them unchanged; [3] in short, a response may be obtained which is not different from that observed in cases in which the heart is beating regularly.

5. In the presence of auricular fibrillation and congestive heart failure, digitalis produces an increase in cardiac output and a decrease in cardiac size and circulation time, and a decrease in venous pressure if it is elevated (earlier [1] and present observations).

6:79 (Aug.) 1928. (*d*) Stewart, H. J., and Cohn, A. E.: Studies of the Effect of the Action of Digitalis on the Output of Blood from the Heart: II. The Effect on the Output of the Hearts of Dogs Subject to Artificial Auricular Fibrillation, ibid. **11**:897 (Sept.) 1932; (*e*) footnote 1. Stewart, Crane, Deitrick and Thompson.[3]

6. In the presence of normal sinus rhythm in congestive heart failure it appears from the observations now being reported, as well as those already recorded,[1] that digitalis increases the cardiac output and decreases the cardiac size, circulation time and venous pressure.

7. In a parallel series of observations on dogs, similar results obtained so far as contraction, cardiac output and cardiac size were concerned.[6b-d]

8. The work of the heart per beat was increased by digitalis in all the cases of heart disease, due to various etiologic factors, which have been studied (earlier [3] and present observations), whether failure was present or not and whether there was a regular rhythm or auricular fibrillation.

Cattell and Gold [7] have recently shown that two digitalis glucosides (ouabain and digitoxin) increase the systolic tension in cats; in short, they increase the force of contraction.

These data may be fitted together into a concept of the action of digitalis. It is apparent that there are certain uniform actions of the drug, namely, a decrease in size and increase in the extent of contraction, an effect on the electrocardiogram and an increase in the work of the left ventricle. Moreover, these occur irrespective of whether the heart is a normal or a diseased one, whether it is compensated or in failure and whether there is a normal sinus rhythm or auricular fibrillation. The net effect of these actions on the cardiac output, however, differs, depending on whether the heart is dilated or not. That is to say, the action of the drug is the same in all instances, but the consequences of the action on the minute volume of blood from the heart are different, depending on whether the heart is small or dilated. These observations show clearly that an effect on size, namely, a decrease, appears to be an important action of the drug. When the size of the heart changes, the cardiac output alters; when a change in size occurs, it appears to override the effect on contraction.[6b,c] If the heart is made too small, the cardiac output decreases, but if the heart is dilated and a decrease in size occurs, the drug brings it to a more appropriate size, and an increase in output occurs. Parallel changes in the velocity of blood flow occur. In all instances which we have encountered, digitalis caused an increase in the work performed by the heart per beat and brought the work accomplished more nearly in line with the size of the organ (figures 7 to 9 in our earlier paper [3] and figures 11 and 12 in this paper). The explanation of these events may be found in Starling's [8] theory dealing with the length of the muscle fibers of the heart. In these cases we have

7. Cattell, M., and Gold, H.: The Influence of Digitalis Glucosides on the Force of Contraction of the Mammalian Cardiac Muscle, J. Pharmacol. & Exper. Therap. **62**:116 (Jan.) 1938.

8. Starling, E. H.: The Linacre Lectures on the Law of the Heart, Given at Cambridge, 1915, London, Longmans, Green & Co., 1918.

demonstrated clear evidence of a change in the size of the heart and an increase in its functional capacity. The correlation of Starr and his associates [5] points to the same notion, and our observations bear them out.

The observations of Cattell and Gold [7] which have been mentioned indicate still another action of digitalis on cardiac muscle, namely, an effect on systolic tension. It appears, however, that this is not the most significant action of the drug, for the effect on size appears to override it, just as it overrides the effect of an increase in the extent of ventricular contraction.[6b,c] There is evidence for this interpretation. In the first place, in normal persons and in certain patients exhibiting heart disease, without congestive heart failure (group 1 in our earlier paper [3]), digitalis decreased the cardiac output and the cardiac size, even though we have reason to believe that the extent of ventricular contraction increased [6a] and that the force of contraction increased; [7] in short, the effect on size in making the pump too small was the predominate one and resulted in a decrease in output, even though an increase in the extent of the contractions and an increase in the force of the contractions were factors influencing the output toward an increase. In the second place, we encountered cases of heart disease without failure (group 3 in our earlier paper [3]) in which the giving of digitalis brought about no change in cardiac size; in them, however, no change in cardiac output occurred. These results give clear evidence that the effect on size is the most significant one, since when it fails to occur, a change in output also is not apparent.

Friedman, Clark, Resnik and Harrison [9] have taken issue with our earlier observations relating to heart failure,[1] because in the rebreathing part of the technic two samples of gas were taken instead of three, and relating to the "time" at which our samples were taken. We used the method which was then available. The patients were selected so that the method would be applicable to them, and to this end we chose those whose lungs were relatively free from rales and who, on trial, were found to rebreathe easily; moreover, we took the samples later than was our custom when studying normal persons.[10] Furthermore, the amount of gas to be rebreathed was reduced, in proportion to the patient's vital capacity, to the amount which, after training, he could take completely. In addition, duplicate observations were made within fifteen minutes, and checks were obtained. It turns out, now that we have come to

9. Friedman, B.; Clark, G.; Resnik, H., Jr., and Harrison, T. R.: Effects of Digitalis on the Cardiac Output of Persons with Congestive Heart Failure, Arch. Int. Med. **56**:710 (Oct.) 1935.

10. In our earlier paper [1] we stated that samples were taken first after a rebreathing period of fifteen seconds. This statement should have been expanded to include those instances in which the rebreathing time was longer.

repeat these observations on patients as nearly like those whom we previously reported on as possible, making use of the three sample technic, that the results are in agreement with those already published by us. These later results, as did the others, reveal an association between cardiac output and cardiac size; in addition, in the latter observations we have added data relating to the velocity of blood flow. In the light of our newer observations there appears to be no reason to discard our earlier ones.

On the other hand, we have stressed the point that, if any underlying pattern of the actions of digitalis is to be detected, as many factors as possible should be kept uniform. To this end we have selected patients as nearly alike as possible for each group. Since, however, cases that are identical in all respects are not encountered in the clinic, we have stressed uniformity of factors that were in our control, namely, giving to all the patients the same amount of the same "batch" of the drug within the same number of hours and making our observations at comparable times with respect to the giving of digitalis; and, finally, since our observations of normal persons indicated that the effects may occur early, we have continued in the belief that these early effects cannot be ignored. Now that we have shown that our former observations need not be discarded, since the new ones follow the same pattern, we have reexamined Harrison's [9] data to discover whether apparently different results were not to be reconciled. He said that he could not detect patterns in his results. The apparent difference so far as cardiac output is concerned between our results and Harrison's may be due to differences in the manner in which the observations were carried out: (*a*) His observations were made at varying times before digitalis was given, while ours were made the day before the drug was given. (*b*) His observations were made at different times after the drug was given, the first observation being made from one to four days after use of the drug was started; in ours (except on two occasions, see the tables) it was made twenty-four hours after the drug was given. (*c*) The patients were given different amounts of the drug, and it is not stated whether it was of the same batch and of the same potency; it was not given to all the patients in a uniform fashion. On the other hand, all our patients received the same amount of the drug, from one "batch," on the same schedule. (*d*) No other drugs were given to our patients which might interfere with recognition or separation of the digitalis effect. (*e*) There is occasioned some doubt about the value of the method he employed in plotting his charts. The average output before the giving of digitalis was taken as a "zero line." This method may be misleading, since observations were made as far ahead of the giving of digitalis as an average of five days; during this time the cardiac output may have changed as a consequence of a change in the patient's state; if this

occurred, data relating to different states of the patient were averaged and taken as a base line and compared with data secured after the drug was given. Plotting the raw data recorded in his tables, as we have done without this procedure, reveals more accurately the effect of the drug. As a consequence there results a resorting of the patients (tables 1 to 3[9]) to show 12 in whom an increase in output occurred (J. E., H. M., A. E., G. B. S., C. M., P. F., L. M., L. M., M. P., A. T., F. B. and S. F.), 5 in whom no change in output was apparent (I. M., M. B., T. K., M. L. and Y. D.) and 5 in whom a decrease in output occurred (M. O., L. W., G. M., A. M., and R. O.) after the giving of digitalis.

It is obvious therefore that the different routines by which his observations and ours were carried out do not make the findings strictly comparable. Nevertheless, when we analyze his data, as already described, by plotting them in the raw, we can detect patterns in his results. He found the cardiac output sometimes increased, sometimes unchanged and sometimes decreased with the giving of digitalis. From his data he said he was unable to establish any correlations with respect to the action of the drug. In certain cases, however, the patients fell into groups similar to those we have described, that is to say, those with an increased cardiac output and those with an unchanged cardiac output. These might have been the ones in whom, in our series, the cardiac size was decreased (group 2[3]) and unchanged (group 3[3]), respectively. On the other hand, the patients in whom he found the cardiac output decreased may be similar to the group we have reported on whose cardiac size was made too small and, as a consequence, whose cardiac output was decreased (group 1[3]). Whether the hearts of his subjects were large or small is not known, and no observations were made relating to the effect of digitalis on the cardiac size. Further speculation on this point is not profitable.

We have not been of the opinion that the action of digitalis can be measured in terms of a single function, such as cardiac output; but it appears that its effects, so far as cardiac output is concerned, can in a measure be correlated with its other effects, namely, the effect on size, on contraction and on work per beat. Furthermore, we have been careful in stating that we do not think that benefit can be gaged in terms of any one effect, such as a change in cardiac output.[1] For, although in the patient with compensated heart disease there are divergent effects on the cardiac output per minute, we have shown one phenomenon common to all, with compensated as well as with uncompensated heart disease, namely, that digitalis increases the work of the left ventricle per beat irrespective of its effect on the total output (our earlier[2] and our present observations).

We find observations of another sort in the literature which give weight to our interpretation of the results of our studies of the action of

digitalis. These relate to the effect of the drug in the heart-lung preparations and in revived human hearts. With regard to the former, Cohn and Steele [11] have reviewed the earlier observations and have contributed data showing that digitalis increases the output of the failing, dilating heart. Peters and Visscher [12] have recently presented data showing that the failing heart suffers a decrease in mechanical efficiency and that digitalis glucosides increase the output and increase the work and "efficiency" of the organ. And, finally, in the case of the revived human heart, Kountz [13] has shown that the exhibition of digitalis to a patient with such a dilated, failing heart resulted in a marked decrease of the diastolic size and an increase in the flow through the coronary arteries.

CONCLUSIONS

From the detailed study of the mechanism of the action of digitalis on the circulation of 42 patients suffering from heart disease (our earlier [3] and our present observations) the following conclusions may be drawn:

The output of blood per minute from the heart which is in failure is diminished, the velocity of the blood flow is less and the heart is larger than when it is in a state of compensation. The work per beat is decreased and is not commensurate with the size of the organ. The venous pressure is in certain instances elevated, and in others it is in the normal range.

Digitalis increases the output per minute of the failing heart, decreases its size and increases the work per beat, so that it more nearly approximates what is expected of it for its size. The circulating blood now moves at a greater velocity. A fall in venous pressure occurs if it was elevated beforehand.

An interpretation of these results in the light of those already reported is that digitalis has the same action on the normal as on the pathologic heart; it decreases the cardiac size, which we interpret as an effect on tone. The amount of the cardiac output which results from this action depends on the initial size of the heart. The amount decreases in the case of a normal heart and increases in the case of a dilated one. Our evidence indicates that digitalis acts in a similar fashion on the normal heart and on those damaged by valvular disease and by myo-

11. Cohn, A. E., and Steele, J. M.: Studies of the Effect of the Action of Digitalis on the Output of Blood from the Heart: I. The Effect on the Output of the Dog's Heart in Heart-Lung Preparations, J. Clin. Investigation **11**:871 (Sept.) 1932.

12. Peters, H. C., and Visscher, M. B.: The Energy Metabolism of the Heart in Failure and the Influence of Drugs upon It, Am. Heart J. **11**:273 (March) 1936.

13. Kountz, W. B.: The Coronary Flow in Hearts of Individuals Dying of Cardiac Insufficiency, Am. Heart J. **12**:490 (Oct.) 1936.

cardial disease unless the myocardial damage is extreme, in which case toxic effects might possibly be elicited at lower concentrations of digitalis.

The effect of digitalis in the presence of auricular fibrillation is similar to that recorded when the rhythm is regular.

The response of hearts damaged by syphilis, arteriosclerosis and hypertension appears to be similar to that observed for hearts damaged by rheumatic fever.

The response of patients whose aortic valves are damaged is not different from that of patients exhibiting mitral involvement.

The decrease in cardiac size appears to be the most important effect of digitalis, the change in cardiac output being a consequence of it.

The lowering of the venous pressure by the administration of digitalis to the patient exhibiting heart failure seems to be dependent on an increase in cardiac output. An increase in cardiac output and work per beat permits the pumping onward of the blood accumulated on the right side so that a proper distribution results.

There are indications that digitalis may benefit certain patients with organic heart disease without heart failure (Christian [14]), but the final proof will depend on clinical observations.

When considered in the light of our data relating to the action of the drug when the heart is normal [1] and to its action when the heart is damaged by organic heart disease but heart failure is not present, the observations now reported with respect to patients with failure, those presenting regular sinus rhythm as well as those exhibiting auricular fibrillation,[8] lead us to restate our original conclusion. Digitalis has similar, perhaps identical, action when the heart is normal and when it is diseased. It decreases the cardiac size and increases the extent of ventricular contraction,[6a] and to these is to be added the effect on systolic tension (Cattell and Gold [7]). The consequence of these actions is that the cardiac output which results differs, depending on the initial difference in the size of the ventricular cavities in the two situations. In the one (the normal heart and the diseased heart which is not failing) it becomes too small; in the other (the diseased heart which is failing) it acquires a suitable size.

These studies demonstrate, however, a more uniform generalization which is applicable to all these situations, namely, that digitalis increases the work of the heart per beat and that with respect to the heart which is failing, it increases the work per beat and makes it more nearly commensurate with the work expected of the heart for its size.

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14. Christian, H. A.: The Use of Digitalis Other Than in the Treatment of Cardiac Decompensation, J. A. M. A. **100**:789 (March 18) 1933.

CLINICAL STUDIES OF RESPIRATION

VII. ADDITIONAL OBSERVATIONS CONCERNING THE VALIDITY OF RESULTS OBTAINED WITH THE BODY PLETHYSMOGRAPH

JAMES A. GREENE, M.D.

L. W. SWANSON, M.D.

AND

R. H. HEEREN, M.D.

IOWA CITY

The use of the plethysmograph in the study of changes in the expiratory volume of the chest has been criticized, and for this reason we wish to report additional observations concerning the validity of this method. Our experiments show that normal persons can be divided into the two following groups: In the first group hyperpnea (voluntary hyperpnea and hyperpnea produced by alteration of the inspired air) is accompanied by a relatively constant oxygen consumption. Spirograms obtained simultaneously with plethysmograms therefore will show the presence or absence of expiratory inflation. In the second group the oxygen consumption is increased during hyperpnea, and the occurrence of expiratory inflation cannot be demonstrated for certain. One may ascertain, however, whether or not expiratory inflation is possible by comparing the volume of the complemental air during rest with the increase produced in the volume of the tidal air during hyperpnea. An increase in the volume of tidal air equal to or greater than that of the complemental air during rest excludes the possibility of expiratory inflation during the observed hyperpnea; whereas if the volume of complemental air during rest exceeds the increase in tidal air by 0.5 to 1 liter or more, expiratory inflation is possible. Proving that expiratory inflation is possible does not signify that it occurs, but we have never observed expiratory deflation beyond that of rest except with coughing or speaking or during forced expiration. Inflation, on the other hand, may occur with any respiratory stimulation.

The results obtained by making simultaneous spirograms and plethysmograms during hyperpnea produced by alteration of the inspired

From the Department of Internal Medicine, State University of Iowa, College of Medicine.

air have been published.[1] The present report is concerned, first, with a comparison of spirograms with plethysmograms made during voluntary hyperpnea and, second, with a comparison of the increase in volume of tidal air during hyperpnea produced by physical exertion with that of the complemental air during rest.

METHOD

For 13 normal men, spirograms and plethysmograms were obtained simultaneously during voluntary hyperpnea.

The increase in tidal air following physical exertion was compared with the volume of complemental air during rest in twenty-nine experiments on 9 young men. The tidal, complemental and reserve air during rest and the vital capacity were measured by means of a face mask attached to a spirometer, the subject being in the supine position. The excursions of the spirometer were recorded and calibrated with a kymograph. Each subject first rested for thirty minutes in the supine position with the face mask in place. The volume of the tidal air during rest was then obtained without his knowledge by diverting the expired air into the spirometer. The volume of complemental air was then estimated at frequent intervals by the usual method. The accuracy of these data for the complemental air was confirmed by obtaining the volumes of both the tidal and the complemental air and subtracting the former from the latter. The average of fifty or more measurements of tidal air was taken as the volume of tidal air during rest, and the average of ten or more measurements of complemental air was taken as the volume of complemental air during rest. The vital capacity was measured in each instance and was found to be proportionate to the volumes obtained for the complemental and the tidal air. The volume of tidal air during hyperpnea following physical exertion was measured with the subject in the supine position for one or two minutes immediately after he had performed ordinary stool stepping as rapidly as possible and for as long as he was physically able. The volume of the tidal air during rest was subtracted from the volume of the largest respiration, and the resulting volume was compared with the volume of the complemental air during rest. According to Peabody and his associates,[2] the greatest pulmonary ventilation occurs for one or two minutes after exertion.

RESULTS

Expiratory inflation occurred in 7 of 13 subjects during voluntary hyperpnea and was demonstrable on both the spirograms and the plethysmograms. In the remaining 6 subjects there was no change in expiratory volume by either method.

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1. Greene, J. A.: Clinical Studies of Respiration: III. Influence on the Expiratory Position of the Chest in Man of an Inspired Air Which Is Low in Oxygen and High in Carbon Dioxide, and of Resistance to Inspiration and to Expiration, Arch. Int. Med. **52**:447-453 (Sept.) 1933.

2. Peabody, F. W.; Sturgis, C. C.; Barker, B. I., and Read, M. N.: Clinical Studies on the Respiration: IX. The Effect of Exercise on the Metabolism, Heart Rate, and Pulmonary Ventilation of Normal Subjects and Patients with Heart Disease, Arch. Int. Med. **29**:277-305 (March) 1922.

It is to be noted from the accompanying table that in all instances the volume of the complemental air during rest exceeded the increase produced in the volume of the tidal air.

COMMENT

The results obtained with simultaneous spirograms and plethysmograms of voluntary hyperpnea corroborate the results reported previously during hyperpnea produced by alteration of the inspired air.[1]

Summary of Data *

Subject	Volume of Complemental Air During Rest, Cc.	Increase in Volume of Tidal Air, Cc.	Difference, Cc.
R. H.	2,216	1,204	1,012
		1,457	759
		1,238	978
		1,996	220
		1,595	621
J. G.	2,443	1,741	702
		1,733	710
		2,073	370
		1,711	732
		1,581	862
		1,619	824
H. B.	3,187	1,579	1,608
		1,428	1,759
		2,076	1,111
		2,040	1,147
		1,547	1,640
		2,371	816
		1,309	1,878
K.	2,195	1,684	511
		1,609	586
		1,637	558
C.	3,085	1,783	1,302
R.	2,989	1,765	1,224
		2,283	706
G.	2,630	1,346	1,284
		1,970	1,160
E.	2,962	2,209	753
		1,723	1,239
P.	2,632	1,607	1,025

* The volume of complemental air during rest exceeded the increase produced in the tidal air by hyperpnea following physical exertion.

The fact that the volume of tidal air during hyperpnea produced by severe muscular exertion does not increase sufficiently to equal the volume of complemental air during rest does not signify that expiratory inflation occurs, but it does show that the expiratory volume of the chest can increase even when the most extreme demands are being made on the respiratory mechanism. In only 2 instances (R. H. and J. G., as shown in the accompanying table) was the difference in the two volumes so slight that expiratory inflation undoubtedly could not have occurred. In both of these experiments the physical exertion was so strenuous that

circulatory collapse appeared imminent. Such a tremendous demand on the respiratory mechanism rarely occurs and was not produced in any of our previous studies.

SUMMARY

Additional observations regarding the validity of results obtained by means of the body plethysmograph are reported. The changes in the expiratory volume of the chest recorded on plethysmograms during voluntary hyperpnea were confirmed by spirograms made simultaneously.

A comparison of the volume of the complemental air during rest with the increase in volume of the tidal air during hyperpnea produced by strenuous muscular exertion shows that expiratory inflation is possible during hyperpnea thus produced.

PNEUMONIA COMPLICATED BY ACUTE PNEUMOCOCCIC HEMORRHAGIC ULCERATIVE GASTROENTERITIS (DIEULAFOY'S EROSION)

REPORT OF TWO CASES

CONLEY H. SANFORD, M.D.

JOHN D. HUGHES, M.D.
AND
JEROME WEEMS, M.D.
MEMPHIS, TENN.

The universal omission from standard American textbooks of mention of gastrointestinal ulcerations complicating pneumonia has prompted us to report 2 cases in which treatment was given to patients in the wards of the John Gaston Hospital. It has occurred to us that this complication may not be as rare as the sparsity of reported cases indicates. Search of the literature available to us reveals reports of only 9 cases, the great majority of these from the French literature.

This complication of pneumonia was first described by Dieulafoy,[1] in 1899. He described 2 cases, the first occurring in a patient with lobar pneumonia in whom severe abdominal pain, hematemesis and melena developed. Autopsy revealed multiple acute ulcerations of the stomach, ranging from the size of a pinpoint to a diameter of 3 mm., most of them being grouped in the pyloric region. By a strange coincidence Dieulafoy had in one of his wards at the same time a patient with lobar pneumonia with abdominal symptoms of unusual severity. On the eighth day of the disease this patient vomited a quart (1 liter) of blood but did not die until the nineteenth day of illness, after pneumococcic meningitis had developed. Examination of the stomach revealed

congestion of the mucous membrane but no active erosions, as in the previous case. The histologic examination of the mucosa showed small hemorrhagic foci, some in the submucous tissue and others, more numerous, in the interglandular tissue. These foci (the origin of the hematemesis) pushed the glands aside and formed distinct masses that were separated from the exterior by a thin layer of mucous membrane. Around the foci no trace of inflammatory reaction was to be seen. The search for micro-organisms was fruitless.

From the Department of Medicine, University of Tennessee, College of Medicine, and of the John Gaston Hospital.

1. Dieulafoy, G.: Gasterite ulcereuse pneumococcique: Grandes hematemeses, in clinique médicale de l'Hôtel Dieu de Paris, Paris, Masson & Cie, 1899, lesson 11, p. 219.

Dieulafoy proposed for this condition the name pneumococcic hemorrhagic ulcerative gastritis.

Chatard,[2] in 1926, collected from the literature reports of 8 cases of gastrointestinal hemorrhage associated with pneumococcic infection. The ages of these patients ranged from 17 to 51 years. Although it was at times difficult to estimate the exact date of onset of the pneumococcic infection, Chatard observed that in the great majority of cases the hemorrhages occurred between the fifth and the twelfth day of the disease, but in Vialard's patient the bleeding took place on the twenty-seventh day of illness.

Chatard classified the gastrointestinal complications of pneumonia as follows:

1. Simple enteric
2. Dysenteric
3. Ulcerating hemorrhagic
   (*a*) Ulcerating
   (*b*) Hemorrhagic

His simple enteric type of complication consisted of tympanites with its accompanying respiratory embarrassment. It is the most common of all complications and is probably the result of profound toxemia rather than of actual invasion of the abdominal viscera by the pneumococci, since it is prevalent in cases of lobar pneumonia in which repeated cultures of the blood are sterile.

The dysenteric type, as the name implies, is a complication in which the symptoms consist of tenesmus, blood-streaked stools and the other well known manifestations of acute dysentery. It is more severe and exhausting than the simple enteric type.

Chatard divided the third type, the ulcerating hemorrhagic type, into two types: The first of these is the ulcerating type, in which there is formation of one or more ulcers of the stomach or intestine without immediate symptoms. The recognition of this variety rests on careful examination of the stools for occult blood, as there is no frank hemorrhage, at least there was none in the case he reported. The case reported by Claus probably was of this type. His patient was ten days convalescent from a pneumococcic infection when ulcers of the lesser curvature of the stomach and of the descending colon ruptured, resulting in generalized peritonitis.

However, 8 of the 9 reported cases and both of our cases were of the frankly hemorrhagic type. An analysis of this group of cases reveals that the predominating initial symptom was abdominal pain of unusual

2. Chatard, J.: A Case of Intestinal Hemorrhage in Pneumococcal Infection, with Clinical Remarks, M. J. & Rec. **123**:453 (April 7) 1926.

severity, which was located in the epigastrium, was more or less constant and was nonradiating. However, in Chatard's case there were pains not only in the epigastrium but also in the lumbar regions. These lumbar pains were probably due to acute hemorrhagic nephritis, which he stated was present as a result of profound toxemia. In this case the pain was intermittent, lasting for periods of thirty minutes, which was in contrast to the continuous type of pain usually observed. Along with abdominal pain, nausea and vomiting were usually present in these cases, but in only about one-third did hematemesis occur. In the remainder there was melena, or enterorrhagia. In 1 of Dieulafoy's cases and in 1 of our own cases both hematemesis and melena occurred.

Besides the abdominal symptoms, these patients usually had all the manifestations of internal hemorrhage, namely, a fall in temperature and blood pressure, restlessness and an increasingly weak, rapid, irregular, thready pulse.

Johnson,[3] in 1929, reported the case of a boy aged 12 years who had a hemorrhage of 1 pint (500 cc.) from the bowel complicating lobar pneumonia which seemed to have been preceded by influenza. An unusual point in his case was that in spite of the hemorrhage the temperature remainded at 104 F. for some time.

REPORT OF CASES

CASE 1.—A. H., a white man aged 53 years, was admitted to the John Gaston Hospital on Feb. 2, 1936, complaining of pain in the left side of the chest, cough, fever and general malaise. The onset of illness was eleven days prior to entry, when the patient contracted a cold accompanied by a cough which became progressively worse. Five days before admission to the hospital he had three distinct chills about eight hours apart, each followed by high fever, aching of the bones and delirium. The night before entry he was awakened by a stabbing pain in the left side of the chest which was made worse by respiration and cough.

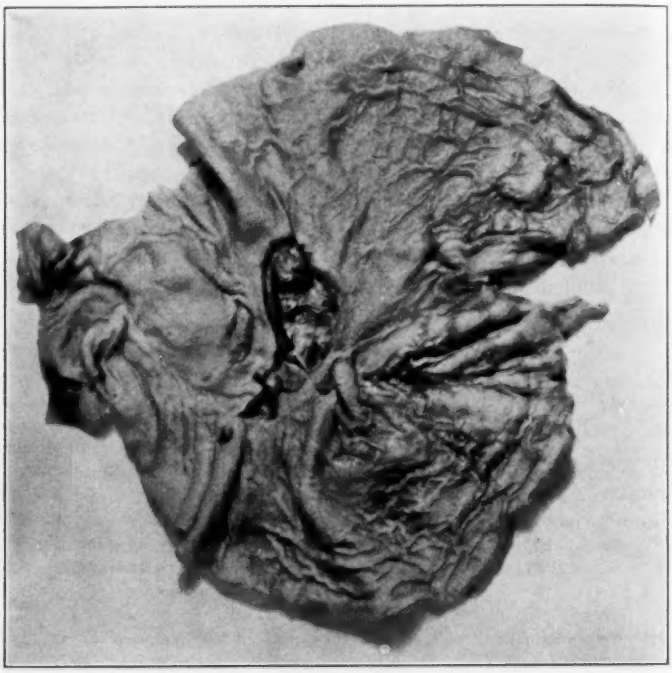
The past and family histories contained nothing of importance relative to the present illness.

Physical examination disclosed all the signs of consolidation of the lower lobe of the left lung. These findings were confirmed by roentgenologic examination, which revealed also areas of increased density characteristic of lobular pneumonia in the upper lobe of the left lung and the lower lobe of the right lung. All the peripheral arteries were moderately resistant to compression. Examination otherwise revealed an essentially normal condition.

The urine contained an occasional granular cast. The red blood cell count and hemoglobin value were slightly below normal; the leukocyte count was 19,000. Later the leukocyte count reached 40,000 and then dropped to 11,000. The percentage of granulocytes remained approximately 89 throughout the disease. The sputum revealed type IV pneumococci. Culture of the blood also showed type IV pneumococci.

3. Johnson, W. M.: Intestinal Hemorrhage as a Complication of Pneumonia, Arch. Pediat. **44**:193 (March) 1929.

The patient's temperature was irregular, ranging from below normal to 105 F. On the eighth day of the disease, signs of empyema on the left side appeared. During the last three days in the hospital the temperature was subnormal continuously, while the pulse and respiratory rates mounted. The blood pressure decreased, ranging between 115 systolic and 50 diastolic and 70 systolic and 30 diastolic. The general trend of the disease showed a progressive increase in severity, with a diminution of the patient's resistance. On the afternoon of February 11, nine days after admission to the hospital, the patient vomited about 2 ounces (60 cc.) of dark red blood and the following day passed a large amount



Photograph of the stomach of our first patient, showing one large ulcer and several smaller ones.

of blood in the stool. He died on the morning of February 13. The clinical diagnosis was: (1) bronchopneumonia, type IV pneumococci; (2) pneumococcic bacteremia, type IV pneumococci; (3) acute pneumococcic hemorrhagic ulcerative gastritis; (4) empyema on the left side, and (5) generalized arteriosclerosis.

Necropsy Observations.—The salient points were scarring of the upper lobe of the left lung, confluent bronchopneumonia of the lower lobe of the left lung, bronchopneumonia of the lower lobe of the right lung, seropurulent empyema on the left and parenchymatous degeneration of the viscera. The stomach and intestines contained large amounts of clotted blood. In the fundus of the stomach (as shown in the accompanying figure) near the center of the lesser curvature

was a large ulceration, 4 cm. in diameter, extending down to the muscular coat, in the base of which was an eroded blood vessel. Adjacent to this ulcer were six smaller and more superficial ulcerations. Sections through the largest ulcer were seen microscopically to contain serum, fibrin, leukocytes, dead cells and bacteria. The margin of the ulcer showed necrosis down to the serosa, with a greatly thickened submucosa.

CASE 2.—P. P., a Negro aged 26 years, was admitted to the John Gaston Hospital on March 17, 1936. His illness began four days prior to entry, with sore throat, general malaise and fever. Soon a cutting pain developed under the left breast which was aggravated by cough and deep inspiration, and he began to raise brownish sputum.

Examination revealed evidences of pneumonia of the lower lobe of the left lung. Those findings were confirmed by roentgenologic examination. The urine contained a few hyaline and granular casts. Slight anemia was present. The leukocyte count was 10,800, with 93 per cent polymorphonuclear cells. Typing of the sputum disclosed type IV pneumococci. Repeated cultures of the blood were sterile. No other abnormal findings were detected.

Two days after admission to the hospital the patient became delirious and remained so until about six days before discharge. At that time also, definite evidences of consolidation of the lower lobe of the right lung appeared. On March 23, the eleventh day of the disease, the patient began to complain of pain in the epigastrium, and examination revealed tenderness and slight muscular rigidity between the umbilicus and the xiphoid. His temperature dropped from 103 to 99 F., and, strange to say, his pulse rate dropped with it. A tentative diagnosis of acute gastrointestinal ulceration was made, and a few hours later the patient passed by rectum about 5 ounces (150 cc.) of blood; the first portion was tarry black and the last dull red. In two days the epigastric tenderness and pain had disappeared and there was no repetition of the bleeding. He was discharged on April 4, the twenty-third day of the disease, in good condition. The clinical diagnosis was: (1) lobar pneumonia (the lower lobes of both lungs) due to type IV pneumococci and (2) acute pneumococcic hemorrhagic ulcerative gastritis or enteritis.

COMMENT

A point of striking coincidence in our 2 cases is that the infecting organisms in both cases were type IV pneumococci. In the first case these organisms were found in the blood stream as well as in the sputum. In the second case the blood was cultured only once prior to the hemorrhage. After the complication, four cultures were sterile. It is most unfortunate that we did not culture the blood daily in this case. In none of the 9 cases reported in the literature was the type of pneumococcus mentioned. Was it mere chance that both our patients were infected with type IV pneumococci, or will future reports by other observers show that this type is particularly likely to cause gastrointestinal ulceration?

In neither of our cases were we able to elicit a history of indigestion, abdominal pain related to meals or any other symptoms suggestive of peptic ulcer antedating the pneumococcic infection. In the first case we

were able to see at necropsy that all the ulcerations were recent. In the second case, in the absence of a history suggestive of peptic ulcer and in the presence of abdominal pain, tenderness and muscular rigidity and of melena, we believe we were justified in making a diagnosis of acute pneumococcic hemorrhagic ulcerative gastritis or enteritis.

It is interesting to note that gastric ulcers occurring in the course of pneumococcic infections have been studied experimentally in the guinea pig. Dieulafoy [4] cited the experiment by Bezançon and Griffon in which the peritoneum of a healthy guinea pig was inoculated with virulent pneumococci. The animal succumbed in twenty-one hours, and postmortem examination revealed petechiae in the mesentery and large intestine and hemorrhagic nodules in the spleen. The musosa of the stomach was studded with about fifteen hemorrhagic erosions. Histologic examination of these erosions showed that the process affected only the mucous and submucous coats and that pneumococci were present in the ulcers, as they were in all the organs. This experiment is particularly interesting from two standpoints: First, it revealed the organisms in the ulcerated tissue. Second, it possibly demonstrated another route by which the pneumococcus may attack the gastric mucosa, namely, by way of the peritoneum. Dieulafoy called attention to Griffon's case, in which acute ulcerations were present in the stomach of a woman who died of pneumonia but no pneumococci could be found in the ulcers. The question was therefore raised as to whether ulceration is invariably due to invasion by pneumococci or to its toxins without invasion. Both of Dieulafoy's patients had complicating pneumococcic peritonitis, but in our patient who came to necropsy there was no evidence of peritoneal infection. The following questions we are not able to answer: Is the presence of the pneumococcus in the wall of the gastrointestinal tract necessary for the production of ulceration, or may it be produced in some instances by pneumococcic toxins? If the presence of organisms is essential to the production of ulceration, must they reach the tissue only through the blood stream, or may they also invade the mucosa from the gastrointestinal canal or by extension from the peritoneum?

In view of our experiences with these 2 cases we consider it important to understand the significance of melena or hematemesis complicating pneumonia. Unfortunately Chatard did not append a bibliography to his article, nor did he note the mortality rate in his own series; but since both of Dieulafoy's patients, Griffon's patient and 1 of our patients died, it is inferred that this complication constitutes a serious prognostic omen.

As to therapy, we have nothing new to offer. Both of our patients received conservative medical treatment for gastrointestinal hemorrhage.

4. Dieulafoy, G.: A Text-Book of Medicine, ed. 15, New York, D. Appleton and Company, 1911, p. 658.

CONCLUSIONS

We have been able to find in the literature reports of only 9 cases of acute pneumococcic hemorrhagic ulcerative gastroenteritis complicating pneumonia. To these we add reports of 2 new cases.

Hematemesis; melena; abdominal pain, tenderness and muscular rigidity, and a fall in blood pressure and temperature with an increase in pulse rate, in the presence of pneumonia, should lead one to suspect this complication.

This important complication of pneumonia is not discussed in any of the standard American textbooks of medicine.

It is probable that the condition is more frequent than is indicated in the literature.

DIABETES INSIPIDUS AS A SIGN OF METASTATIC INVOLVEMENT OF THE SUPRAOPTICO-HYPOPHYSIAL SYSTEM

MITCHELL BERNSTEIN, M.D.

MATTHEW T. MOORE, M.D.

AND

DAVID B. FISHBACH, M.D.

PHILADELPHIA

Diabetes insipidus as a clinical manifestation has long been a subject of interest and controversy. The latter has resulted in an accumulation of clinical and experimental data which has tended to clarify the concept of the mechanism of diabetes insipidus. A complete review of the literature of the subject of diabetes insipidus would literally inundate the reader with watery references. However, for want of space, reference to several notable surveys, presented from different points of view, will indicate the extent of the literature and serve as source material.

Staemmler,[1] in 1932, in an extensive review of the subject up to that time, presented evidence indicating that isolated lesions involving the posterior and intermediate lobes of the pituitary body or the hypothalamus may lead to diabetes insipidus. Roussy and Mosinger [2] and Leschke,[3] in 1933, in separate reviews showed the evidence favoring the hypothalamic origin of diabetes insipidus. More recently the outstanding experimental investigations of Ranson and his group of workers [4] have drawn together the loose ends and have tended to present

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From the Jewish Hospital and from the John L. Eckel Memorial Laboratory of Neuropathology.

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1. Staemmler, M.: Diabetes insipidus und Hypophyse, Ergebn. d. allg. Path. u. path. Anat. **26**:59, 1932.

2. Roussy, G., and Mosinger, M.: Le tuber cinereum et son rôle dans les principales fonctions du métabolisme; métabolisme de l'eau, des glucides et des lipides, Ann. de méd. **33**:193, 1933.

3. Leschke, E.: Diabète insipide et système hypothalamo-hypophysaire, Ann. de méd. **33**:261, 1933.

4. (*a*) Fisher, C.; Ingram, W. R., and Ranson, S. W.: The Relation of the Hypothalamico-Hypophyseal System to Diabetes Insipidus, Arch. Neurol. & Psychiat. **34**:124 (July) 1935. (*b*) Fisher, C.; Ingram, W. R.; Hare, W. K., and

(Footnote continued on next page)

a harmonious concept of the pathogenesis of diabetes insipidus. They have said:

> The evidence from this investigation supports the theory that diabetes insipidus is a hormonal disturbance, caused by a deficiency in the secretion of the antidiuretic principle by the pituitary gland. The view is set forth that the supraoptico-hypophyseal system sends secretory impulses to these divisions of the hypophysis and that damage to this system at one of three points, the nucleus, the fiber tract and the pars intermedia and pars neuralis, results in diabetes insipidus.

Findley [5] (1937) has traced the origin of the conflicting theories concerning diabetes insipidus and has shown the relation of this disorder to the function of the thyroid gland.

Diabetes insipidus, representing a disturbance in the normal functioning of the supraopticohypophysial system, may be due to many conditions which implicate that system. Fink [6] (1928), reviewing the necropsy records of 107 patients with diabetes insipidus, cited the following etiologic factors: functional nervous disturbances, such as hysteria, migraine, epilepsy and severe fright; pregnancy; injuries to the base of the skull; syphilitic basal meningitis; tuberculous meningitis; convalescence from acute infectious diseases; epidemic encephalitis; tumors of the midbrain, the hypophysis and the region of the third ventricle; metastatic lesions involving the posterior lobe of the pituitary body and gliomas of the optic chiasm. Of the 107 patients, 63 per cent had a tumor at the base of the brain or in the posterior cranial fossa which involved more than one structure at the base of the brain and hence was not of localizing value as regards the appearance of diabetes insipidus.

Ranson S. W.: The Degeneration of the Supraoptico-Hypophyseal System in Diabetes Insipidus, Anat. Rec. **63**:29, 1935. (*c*) Ingram, W. R., and Barris, R. W.: Diuresis Associated with Direct Stimulation of the Hypophysis, Endocrinology **19**:432, 1935. (*d*) Ingram, W. R.; Fisher, C., and Ranson, S. W.: Experimental Diabetes Insipidus in the Monkey, Arch. Int. Med. **57**:1067 (June) 1936. (*e*) Fisher, C., and Ingram, W. R.: The Effect of the Feeding of Thyroid Extract or Salt and of Thyroidectomy on the Fluid Exchange of Cats with Diabetes Insipidus, ibid. **58**:117 (July) 1936. (*f*) Ingram, W. R., and Fisher, C.: The Relation of the Posterior Pituitary to Water Exchange in the Cat, Anat. Rec. **66**:271, 1936. (*g*) Fisher, C., and Ingram, W. R.: The Effect of Interruption of the Supraoptico-Hypophyseal Tracts on the Antidiuretic, Pressor and Oxytoxic Activity of the Posterior Lobe of the Hypophysis, Endocrinology **20**: 762, 1936. (*h*) Fisher, C.: The Site of Formation of the Posterior Lobe Hormones, ibid. **21**:19, 1937. (*i*) Ingram, W. R., and Fisher, C.: The Effects of Thyroidectomy, Castration, Anterior Lobe Administration and Pregnancy upon Experimental Diabetes in the Cat, ibid. **21**:273, 1937.

5. Findley, T.: Thyroid-Pituitary Relationship in Diabetes Insipidus, Ann. Int. Med. **11**:701, 1937.

6. Fink, E. B.: Diabetes Insipidus: A Clinical Review and Analysis of Necropsy Reports, Arch. Path. **6**:102 (July) 1928.

In 14 per cent of the cases reviewed by Fink there was a discrete metastatic carcinomatous nodule limited to the posterior lobe of the hypophysis or to the infundibulum. He stated, "When polyuria develops in a case of malignancy, it is almost a pathognomonic sign of a metastasis in the posterior lobe of the hypophysis." In view of the evidence that involvement of any portion of the supraopticohypophysial system may produce diabetes insipidus, it is well to consider the occurrence of polyuria in a patient with a malignant growth as an indication of metastatic invasion of the whole or of a part of that system.

Since the publication of the review of case reports collected from the literature by Fink,[6] other cases have been reported in which diabetes insipidus occurred in patients with metastatic lesions involving the hypothalamicohypophysial system. Futcher[7] reported a case of diabetes insipidus due to metastatic involvement of the hypothalamus (the pituitary body remaining entirely free from metastasis) secondary to primary carcinoma of the lung. Elmer, Kedzierski and Scheps[8] reported a case of hypernephroma with metastasis to the hypothalamus producing diabetes insipidus. Grassmann[9] described a case of diabetes insipidus following carcinoma of the breast in which metastatic lesions occurred in the posterior lobe of the pituitary body and in the tuber cinereum, with little involvement of the anterior lobe and none of the diencephalon. Arnstein,[10] who has stated the belief that the posterior lobe of the pituitary body is intimately associated with control of water metabolism, reported 4 cases of diabetes insipidus resulting from metastatic carcinosis of the posterior lobe of the pituitary body. In two of the cases the condition was secondary to carcinoma of the breast, and in 2 other cases it was secondary to bronchogenic carcinoma. Multiple metastases to the brain developed in 2 cases. The posterior lobe was involved in all the cases, the stalk in 2 cases, the anterior lobe in 2 cases and the capsule in 1 case. In a report of 3 cases of diabetes insipidus Biggart[11] described 1 case that was due to multiple carcinomatous metastases to the brain, involving the whole of the posterior lobe of the pituitary

7. Futcher, T. B.: Diabetes Insipidus and Lesions of the Mid-Brain: Report of a Case Due to a Metastatic Tumor of the Hypothalamus, Am. J. M. Sc. **178**: 837, 1929.

8. Elmer, A. W.; Kedzierski, J., and Scheps, M.: Ein Fall von Diabetes insipidus verursacht durch eine Metastase eines Hypernephroms im Zwischenhirn: Beitrag zur Pathogenese des Diabetes insipidus, Wien. klin. Wchnschr. **41**:591, 1928.

9. Grassmann, W.: Diabetes insipidus bei Tumormetastasen in der Hypophyse, Frankfurt. Ztschr. f. Path. **42**:384, 1931.

10. Arnstein, A.: Diabetes insipidus bei metastatischer Karzinose der Hypophyse, namentlich des Hinterlappens bei primärem Bronchus- und Mammakarzinom, Med. Klin. **29**:1679, 1933.

11. Biggart, J. H.: Diabetes Insipidus, Brain **58**:86, 1935.

body, the infundibulum, the hypothalamus and a small part of the anterior lobe of the pituitary body. The primary growth was presumably in the alimentary tract. Macchioro [12] reported a case of metastatic bronchogenic carcinoma involving the hypophysial system and producing diabetes insipidus. In the case of diabetes insipidus reported by Urechia [13] the primary lesion was an alveolar carcinoma of the stomach, with metastasis to the entire posterior lobe of the pituitary body, a large part of the intermediate lobe and parts of the anterior lobe and tuberal region.

In the light of so much excellent material on this topic, we lay claim to justification for presenting the following case report because of the unusual features of both hematogenous and lymphogenous metastases of a bronchogenic carcinoma, the former producing diabetes insipidus by involvement of the posterior lobe of the pituitary body and of the infundibulum and the latter resulting in involvement of the serous membranes of the abdominal and thoracic organs with tubercles.

REPORT OF A CASE

History.—W. S., a man aged 64 years, a baker, entered the Jewish Hospital on Dec. 3, 1936, complaining of polydipsia, polyuria and anorexia of four months' duration. His past medical history was unimportant. He noticed the symptoms in August and several weeks later observed that he was growing weak. He ate little solid food but drank 3 or 4 quarts (3 or 4 liters) of milk daily, in addition to several glasses of water. However, there was no loss of weight, the patient maintaining his usual average of 160 pounds (72.6 Kg.). There was no pain, vomiting, hematemesis or melena.

General Examination.—On admission to the hospital the patient was fairly well nourished. The routine physical examination revealed no abnormality except a coated tongue, a foul breath and an area of bronchovesicular breathing on the left side of the chest at the seventh interspace posteriorly. The blood pressure was 120 systolic and 70 diastolic. The temperature varied from 97 to 100 F.

Course.—The patient remained in the hospital thirty-five days without showing any definite improvement. The daily urinary output varied from 1,000 to 4,890 cc. One cubic centimeter of solution of posterior pituitary U. S. P. given hypodermically on December 10 and 1 cc. of solution of posterior pituitary double U. S. P. strength on December 12 caused a marked diminution in the excretion of urine. However, after each injection the patient became apprehensive and agitated. The pulse rate increased and the face became flushed. He subsequently refused all further medication of this nature.

On Jan. 7, 1937, the patient left the hospital unimproved, his weight at that time being 155 pounds (70 Kg.).

The following day, January 8, the patient became unconscious while walking along the street and was brought immediately to the hospital. Examination dis-

12. Macchioro, G.: Su un caso di diabete insipido da tumore metastatico della regione ipofisaria, Minerva med. **1**:668, 1935.

13. Urechia, C. I.: Cancer métastatique de la région hypophyso-tubérienne avec diabète insipide, Paris méd. **2**:129, 1936.

closed rotatory nystagmus and left hemiplegia. The blood pressure was 150 systolic and 60 diastolic. Pulmonary edema supervened, and death occurred at 4:05 a. m. the following morning.

Laboratory Data.—Many examinations of the urine showed that the specific gravity varied from 1.002 to 1.010; there was a trace of albumin but no sugar. On microscopic examination a few white blood cells were observed occasionally. The volume of urine varied from day to day, the minimum (1,000 cc.) being voided on December 23 and the maximum (4,890 cc.) on December 7.

Eight blood counts from Dec. 4, 1936, to Jan. 6, 1937, showed that the hemoglobin value varied from 85 to 104 per cent, the erythrocyte count varied from 4,500,000 to 5,350,000 per cubic millimeter, the leukocyte count averaged 8,700 per cubic millimeter and the average differential count showed 74 per cent polymorphonuclear cells, 24 per cent lymphocytes and 2 per cent eosinophils.

Chemical analysis of the blood on December 4 showed a sugar content of 81 mg. per hundred cubic centimeters and a urea nitrogen content of 16 mg. A sugar tolerance test gave the following values: 81 mg. during fasting, 111 mg. at one-half hour, 206 mg. at one hour and 111 mg. at two hours. All specimens of urine during this test were free from sugar.

A phenolsulfonphthalein test, made on December 16, indicated a 55 per cent output for the first hour and a 10 per cent output for the second hour. The Fishberg test gave the following results: first specimen, 166 cc., with a specific gravity of 1.010; second specimen, 57 cc., with a specific gravity of 1.013, and, third specimen, 50 cc., with a specific gravity of 1.010. A urea clearance test showed a 70 per cent normal function with the first specimen and a 64 per cent normal function with the second.

Wassermann tests of the blood and spinal fluid gave a negative reaction. The colloidal gold curve was 0000000000.

Fractional gastric analysis showed the following:

	Minutes							
Residuum	15	30	45	60	75	90	105	120
Free hydrochloric acid.	10	25	30	35	50	70	70	80	80
Total acidity	25	35	65	70	70	90	100	110	105

The microscopic study of the various gastric specimens revealed essentially no abnormality.

Roentgen studies, including the skull, chest, gastrointestinal tract and gallbladder, were reported as follows:

On December 7 the sella turcica presented a normal appearance. There was no evidence of erosion or destruction of the floor, clinoid processes or dorsum sellae. No encroachment was noted in the phenoid sinus. It measured 5 by 10 mm., which was within normal limits. There was slight calcification in the pineal gland, which was not displaced in the lateral view. There was some condensation of bone in the frontal area, which was of no etiologic importance as to the presence of any intracranial lesion.

The heart, right lung and diaphragm were normal. A dense area in the upper field of the left lung was limited to the interlobar fissure and presented the appearance of an inflammatory consolidation, presumably subacute interlobar pleurisy associated with the pneumonitis in the adjacent fields.

The cholecystogram was negative, as was the roentgenogram of the gastrointestinal tract except for signs of an irritable colon.

On January 4 the calcium content of the blood was 11.2 mg., and the phosphorus content was 4 mg. per hundred cubic centimeters. On January 8 the

sugar content was 107 mg., the urea nitrogen content was 20 mg. and the carbon dioxide-combining power was 55 volumes per cent.

Gross Postmortem Observations.—The body was that of an obese aged man. There was no edema of the lower extremities.

There was no excess fluid in the serous cavities. A normal amount of light amber pericardial fluid was present. The parietal pericardium, especially the portion covering the left ventricle, showed a number of firm, elevated, grayish white, sharply demarcated nodules, 1 or 2 mm. in diameter. There were no nodules on the visceral pericardium except in one area near the base of the heart in the region of the interventricular septum.

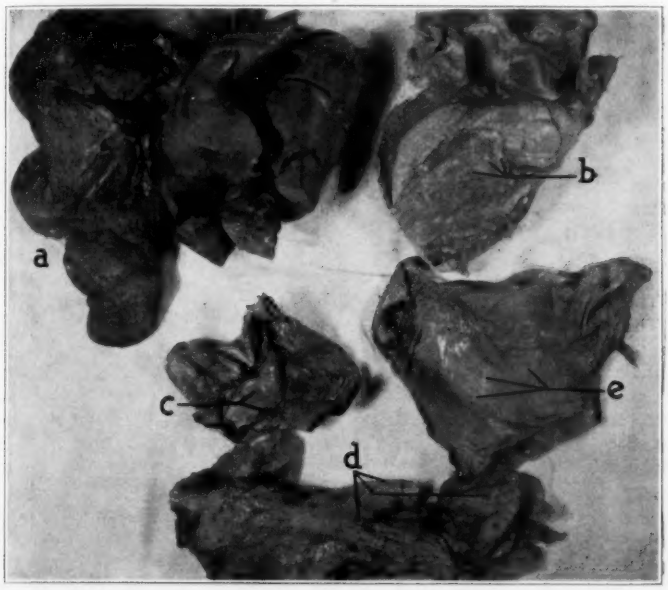

Fig. 1.—Gross specimens of (*a*) the right and left lungs, (*b*) heart and pericardium, (*c* and *e*) diaphragm and parietal peritoneum and (*d*) serosal surthe left lung showed that the alveoli were filled with large epithelioid cells, varying the serous membranes.

The coronary arteries showed marked atheroma with sclerosis. There was no occlusion. The aorta showed slight atheromatous change (not syphilitic).

Both the visceral and the parietal pleura, to a more marked extent on the left side, showed numerous elevated, firm, grayish white nodules, 1 to 3 mm. in diameter, in some instances extending into the pulmonary parenchyma.

In the left lung, in the lower portion of the upper lobe, there was a firm, almost completely consolidated area 8 to 9 cm. in diameter, which grossly gave the appearance of a lobar pneumonic area during the stage of gray hepatization.

However, it was not moist, so that this grayish white, solidified area appeared to be a malignant growth. It did not lead directly into a bronchus, on gross examination.

The left bronchus, near its bifurcation, showed a firm, grayish white nodule, the size of a small pea, extending into the pulmonary tissue. This was evidently the site of primary bronchogenic carcinoma. The rest of the left lung was crepitant and showed moderate congestion and edema. No old or recent areas of tuberculosis were observed within the pulmonary tissue.

The right lung showed marked edema and slight congestion.

There was no free peritoneal fluid. The entire parietal peritoneum was studded with numerous gray, flattened nodules, 1 to 3 mm. in diameter. Similar nodules were present on both surfaces of the diaphragm. These nodules in the peritoneal cavity were most numerous on the left parietal wall and extended into the pelvic peritoneum covering the serosa of the urinary bladder.

The cecum and ascending colon showed a few nodules, 1 or 2 mm. in diameter, on the serosal surface. The lymph nodes were not enlarged.

The prostate showed slight hyperplasia. It was moderately firm but did not appear grossly to harbor a malignant growth.

The liver was slightly enlarged and showed moderate congestion. On the posterior portion of the left lobe, near the periphery, were two grayish yellow nodules, 3 and 6 mm., respectively, in diameter, showing slight central umbilication.

The gastrointestinal tract was normal. There was no ulceration or evidence of malignant growth. There were a few tiny malignant nodules on the serosa of the cecum.

The skull revealed no abnormality.

The spinal fluid was clear. There was cerebral edema, so that the convolutions were flattened. There was marked congestion of the veins on the surface of the brain. The pituitary body was grossly of normal size. The sella turcica was normal. The blood vessels appeared fibrotic. There was an area of recent softening in the right hemisphere. A small area which resembled a tubercle was observed in the cortex in the left upper parietal area. An area which also resembled tuberculoma was seen in the temporal lobe on the right side.

Histologic Postmortem Examination.—Sections of the malignant growth in the left lung showed that the alveoli were filled with large epithelioid cells, varying markedly in size and exhibiting acinar formation. These cells contained large hyperchromatic nuclei, and many showed mitotic figures. Papillary arrangement of the cells was noted in other areas. The growth was a bronchogenic adenocarcinoma showing marked regressive changes.

Examination of the metastatic nodules in the pericardium, liver, peritoneum and other involved organs showed a striking resemblance to the original malignant growth in the left lung.

The gross examination of cut tissues of the brain showed highly stained metastatic nodules with a predilection for the cortex. There was no apparent involvement of the white matter. The diameter of the nodules varied from 0.5 mm. or less to 6 mm. The larger nodules were observed in the motor cortex. Small metastatic nodules were seen throughout the cerebellum.

The meninges were thickened, and over the sulci the subarachnoid space contained a cellular exudate consisting of round cells and pigment-bearing histiocytes. At the periphery of one large nodule in the motor area there was seen for a considerable distance a single layer of epithelial cells occupying the position of the pia. This single layer, in all appearances, looked like the epithelial lining of a bronchus. From this single layer there were invaginations of the epithelial

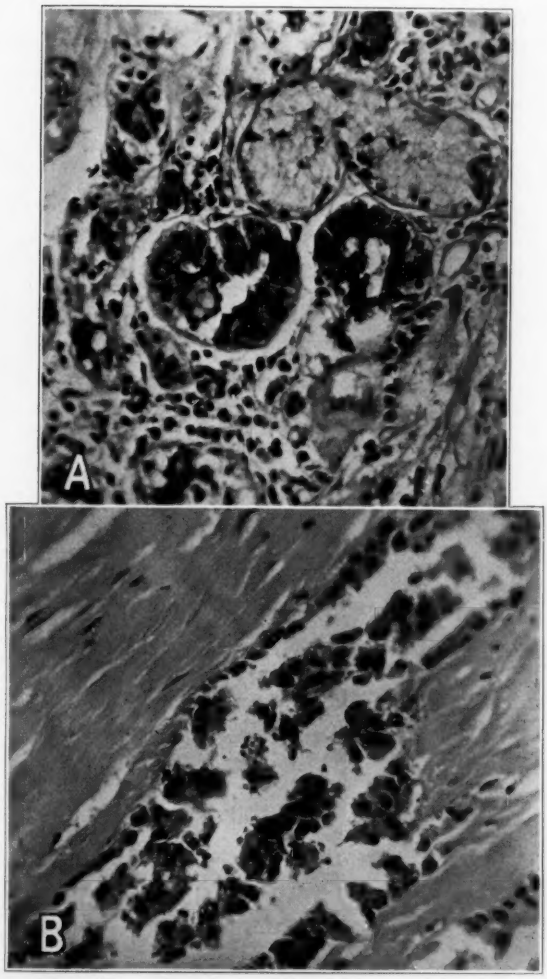

Fig. 2.—*A*, section of the lung, showing two acinar formations of malignant cells. *B*, section through a metastatic nodule involving the pericardium. Hematoxylin and eosin stain; high power.

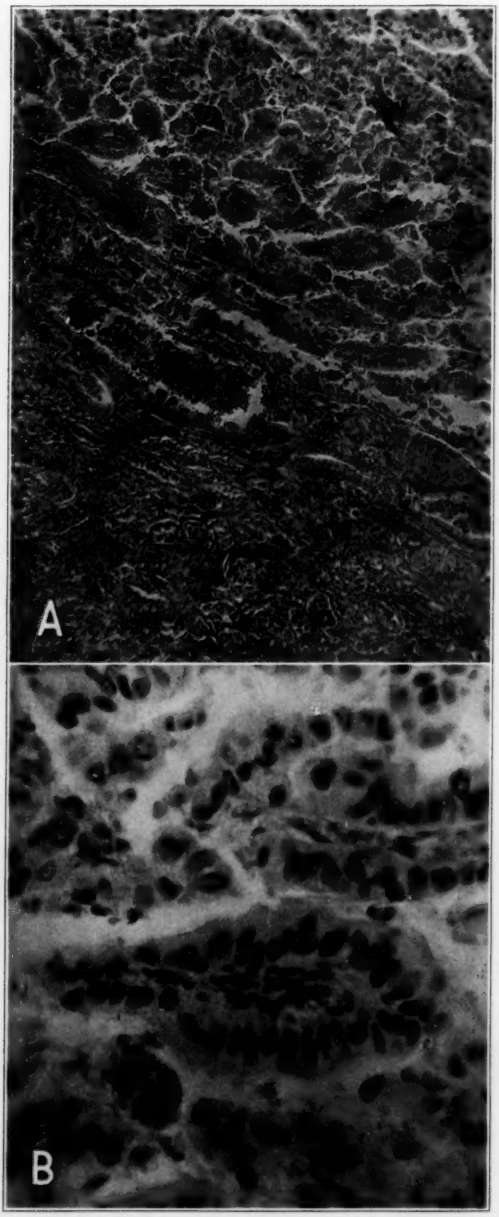

Fig. 3.—*A*, section showing the division between the anterior and the posterior lobe, with the pars intermedia lying diagonally between the two lobes. The upper portion shows the metastatic involvement of the posterior lobe; low power. *B*, high power view of the metastatic cells in the posterior lobe, showing the character of the cells and their arrangement.

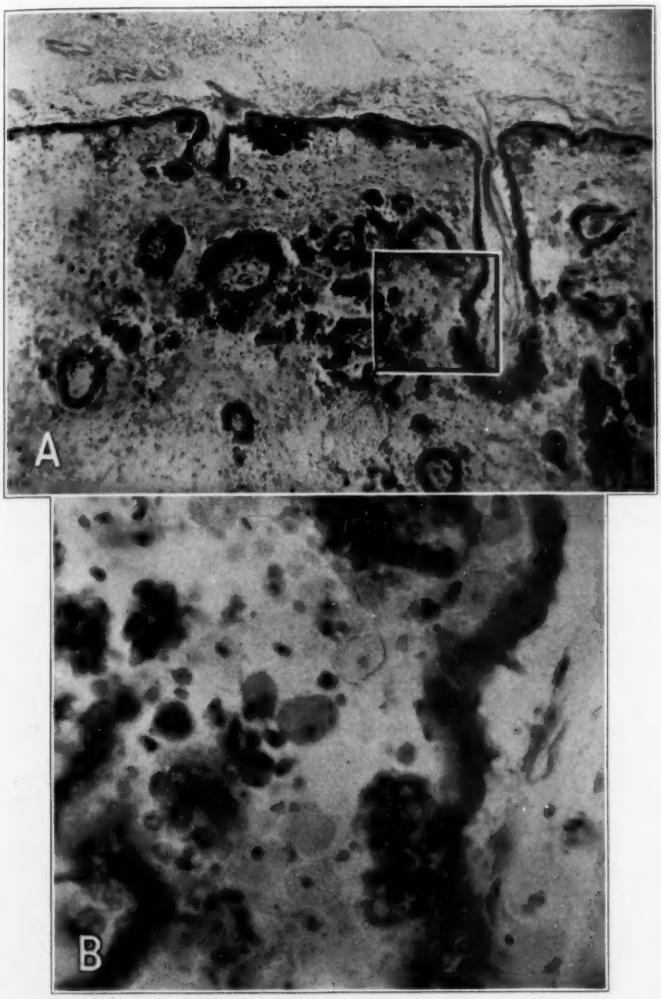

Fig. 4.—*A*, a section (low power) through the cerebral cortex which includes the first, second and third layers, showing complete absence of a normal cortical architecture. There is a single layer of metastatic carcinoma cells on the surface of the cortex, with invaginations here and there simulating the epithelial lining and secretory glands of a bronchus. There are also groups of metastatic cells forming acini. *B*, high power view of the blocked area in *A*, showing the character of the metastatic cells. Several gitter cells can be seen in this section. Toluidine blue stain.

cells which extended into the lamina zonalis, producing what appeared to be glandular, tubular formations.

The cells in the nodules were made up of deeply staining nuclei and cytoplasm and were arranged usually in a single layer in tubular or acinar formation. The cells were columnar, and others appeared to be flat squamous epithelial cells. In the cortex there were many compound granular cells in the areas invaded by these nodules. The cortical architecture showed a disturbance in the number of ganglion cells, with small areas devoid of normal cellular elements. The ganglion cells showed evidence of chronic disease. A moderate degree of marginal gliosis and increased gliosis of the cortex and subcortex were noted. Neuronophagia was present to a slight degree. The larger vessels showed metachromasia, involving the media in particular. There was no evidence of atheroma formation. The walls of the vessels of moderate and of small size presented hyalinization. The capillaries had a thickened endothelium and in the region of the metastatic nodules showed this to a marked degree.

In view of the clinical picture of diabetes insipidus, the question of the anatomic locations of the various lesions had to be considered. The entire posterior lobe of the pituitary body was completely destroyed as the result of invasion by carcinomatous tissue. Cells in this new tissue were arranged in places in acinous formation and in other places were without regular arrangement. The cells were frequently larger than the usual epithelial cell and occasionally contained large hyperchromatic nuclei, some of which were undergoing mitosis. While there was fairly sharp localization to the posterior lobe, at its connection with the anterior portion slight invasion into the glandular portion of the pituitary body was visible. For the most part the new growth was restrained within the capsule, but occasionally some of the tumor cells were seen in the capsule itself. The stalk of the pituitary body was filled with metastatic cells. A comparison of the tumor growth within the pituitary body with the original lesion in the lung and with metastasis to some of the other organs revealed a remarkable resemblance.

Serial sections of the hypothalamic region and the region of the third ventricle were carefully examined for evidences of tumor tissue. Microscopic islands of carcinoma were present in the entire cerebrum and cerebellum, including the meninges. The region of the third ventricle and of the supraoptic nuclei, however, was entirely free from carcinoma. There were comparatively recent hemorrhages in this area, but these, because of their recent origin, did not indicate any long-standing condition.

Diagnosis.—The following diagnosis was made: parenchymatous degeneration of the heart; coronary atherosclerosis; primary bronchogenic carcinoma of the left lung, with metastasis to the pleura, diaphragm, peritoneum, pericardium, liver, brain and pituitary body; congestion and edema of the right lung; congestion of the spleen; chronic atrophic splenitis; nephrosclerosis; congestion of the kidneys; cloudy swelling, congestion and metastatic carcinoma of the liver; slight hyperplasia of the prostate; terminal petechial hemorrhages in the subthalamic region; cerebral arteriofibrosis, with chronic cell change; metastatic bronchogenic carcinoma of the brain, and metastatic involvement of the posterior lobe of the pituitary body and of the infundibulum.

COMMENT

This patient entered the hospital presenting only the symptoms of diabetes insipidus. The history, the physical examination and the

laboratory data gave no definitive clues as to the etiologic factor responsible for the disturbance in water metabolism. Examination of the chest revealed an area of bronchovesicular breathing on the left side at the seventh interspace posteriorly. This was confirmed by the roentgenographic findings, which, however, were interpreted as indicating inflammatory and not malignant involvement. There was no evidence of a malignant process from an a priori consideration. In cases in which a diagnosis of a malignant process has been definitely established, for instance, after operation for carcinoma of the breast or in cases in which an active malignant process has been conclusively demonstrated by biopsy or roentgenographically, and in which diabetes insipidus has supervened, the conclusion is warranted, as Fink [6] has maintained, that the supraopticohypophysial system has been involved. Conversely, on the basis of our case, diabetes insipidus may be considered as the manifestation of a metastatic involvement of the supraopticohypophysial system secondary to an undetermined primary malignant growth elsewhere, which should be definitely ascertained by the clinician or ruled out as one of the etiologic factors producing the diabetes insipidus.

The assumption of a primary lesion elsewhere and its early apprehension are obviously important as regards therapy. Boyd [14] has stated:

> Lung tumors tend to spread and the secondary growths may be the first announcement that there is anything wrong with the patient. Spread is threefold (1) through the lung, (2) to the lymph nodes, and (3) to distant organs. Spread to distant organs is very common. The order of frequency is as follows: (1) liver, (2) brain and bone, (3) kidney and adrenal; less commonly the pancreas, thyroid, etc., may be involved. The brain metastasis is often mistaken clinically for a primary cerebral tumor, because the cerebral symptoms may precede the pulmonary ones.

In addition to the amelioration of the polyuria by the use of solution of posterior pituitary, more lasting benefit may be expected by irradiation of the metastatic lesion involving the hypothalamicohypophysial area, as well as appropriate attention to the primary malignant growth. Desbuquois [15] reported a case of cervical malignant lymphogranulomatosis in which the growth receded for a period of one year after irradiation of the involved glands, only to be followed with a recurrence complicated by diabetes insipidus. Roentgen treatment of the cervical lymph nodes and of the pituitary and hypothalamic region resulted in marked amelioration of symptoms; the urinary output decreased from 12 to 13 liters per twenty-four hours previous to irradiation to about 2 liters after irradiation.

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14. Boyd, W.: Textbook of Pathology, ed. 2, Philadelphia, Lea & Febiger, 1934, pp. 484-486.

15. Desbuquois, M. B.: Sur un cas de lymphogranulomatose maligne compliquée de diabète insipide, Arch. med.-chir. de Province **26**:25, 1936.

The gross appearance of the metastatic nodules involving the pleura, parietal pericardium and serous membranes of the abdominal cavity was not unlike that of miliary tubercles; indeed, on macroscopic inspection the nodules in the cerebrum and cerebellum were first thought to be tubercles. The histologic examination showed them to consist of malignant cells similar morphologically to those of the primary bronchogenic carcinoma. According to Karsner,[16] miliary carcinosis manifests itself by innumerable nodules, a few millimeters in diameter, that are translucent and white, that bulge in the cut surface and that usually are situated along the course of the lymphatic vessels.

The metastatic invasion of the brain in our case was most likely hematogenous. Winkelman and Eckel,[17] in discussing the various modes of dissemination of carcinoma to the nervous system, enumerated the adherents to the theories of lymphogenous and of hematogenous dissemination, or both, and of spread by direct extension. They concluded, however, that metastasis from distant parts (thoracic and abdominal organs) can be best explained by assuming that the blood stream acts as the channel of transmission to the brain. They substantiated their claim by citing a case of primary carcinoma of the breast in which cancer cells were found within the blood vessels of the brain.

In view of the reports in the literature of the hypothalamic origin of diabetes insipidus, careful study of this region was carried out, but no evidence of metastasis could be found. There were recent capillary hemorrhages in the ventromedial hypothalamic nuclei which, however, were terminal in nature. The entire posterior lobe of the pituitary body and the infundibulum were filled with metastatic carcinoma; part of the capsule and a minute portion of the anterior lobe of the pituitary body were also invaded. The polyuria in this case, therefore, was due to infundibulohypophysial involvement alone.

SUMMARY AND CONCLUSION

A case of diabetes insipidus in which the history and clinical study failed to reveal the etiologic factor is presented.

Postmortem study showed primary bronchogenic carcinoma involving the left lung, with metastasis to the serous membranes of the thoracic and abdominal organs and to the cerebrum, cerebellum, hypophysis and infundibulum, with sparing of the hypothalamus.

16. Karsner, H. T.: Human Pathology, Philadelphia, J. B. Lippincott Company, 1926, pp. 581-582.

17. Winkelman, N. W., and Eckel, J. L.: Metastatic Carcinoma of the Central Nervous System, J. Nerv. & Ment. Dis. **66**:1 and 133, 1927.

In the absence of conclusive evidence as to the etiologic factor in a case of diabetes insipidus, it is suggested that a masked malignant process be suspected, that an effort be made to establish the primary source and that, on an empiric basis, irradiation be given to the hypothalamicohypophysial area.

Dr. N. W. Winkelman made the neuropathologic study.

1813 Delancey Street.

CHEMICAL FACTORS CONCERNED IN THE FORMATION OF GALLSTONES

RALPH E. DOLKART, M.D.*

K. K. JONES, PH.D.

AND

CLARENCE F. G. BROWN, M.D.

CHICAGO

It is well known that in certain of the domestic animals, notably dogs, sheep, cats and rabbits, gallstones rarely form spontaneously and cannot be produced experimentally. Schlotthauer and Stalker [1] reported the occurrence of bilirubin stones in 2 of 155 dogs studied at autopsy. Ivy [2] has observed bilirubin stones in only 1 of 500 dogs whose gallbladders were opened routinely. Approximately 150 dogs were used during the course of our experiments, and calculi were never observed. The spontaneous occurrence of true cholesterol stones in dogs, sheep, cats and rabbits has not been reported. In contradistinction to these animals are certain others—chiefly human beings, oxen and hogs—in which biliary calculi occur frequently. A satisfactory explanation of the differences in the bile of these two groups of animals would do much toward accounting for some of the factors concerned in the production of gallstones.

In 1903 Harley and Barratt [3] reported a series of observations in which gallstones from human beings placed in the gallbladders of dogs dissolved over varying periods. These results confirmed the original observations made by Labes [4] a few years previously. Since the original reports, numerous other workers [5] have obtained similar findings. In

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* Searle Fellow in Clinical Medicine.

From the Department of Medicine and the Department of Physiology, Northwestern University Medical School, and St. Luke's Hospital.

1. Schlotthauer, C. F., and Stalker, L. K.: Cholelithiasis in Dogs, J. Am. Vet. M. A. **41**:758, 1936.

2. Ivy, A. C.: Personal communication to the authors.

3. Harley, V., and Barratt, W.: An Experimental Enquiry into the Formation of Gallstones, J. Physiol. **29**:341, 1903.

4. Labes, cited by Brockbank, E. M.: On Gallstones, Philadelphia, P. Blakiston's Son & Co., 1896, p. 67.

5. Naunyn, B.: A Treatise on Cholelithiasis, translated by A. E. Garrod, London, New Sydenham Society, 1896. Frerichs, F. T.: Klinik der Leberkrankheiten, Braunschweig, F. Vieweg & Sohn, 1861, vol. 2, p. 487. von Hause-

1930 Walsh and Ivy [6] determined the rates of dissolution of human gallstones in a large series of dogs under varying conditions. They concluded that the rate of solution of a human gallstone in the dog's gallbladder is not significantly altered from the normal by feeding high fat, high cholesterol diets. A slight increase in the rate of solution was reported on the addition of bile salts and cod liver oil to the diet. They further observed that factors which diminished the flow of bile into and out of the gallbladder or which diminished the concentrating power of the wall of the gallbladder, as when cholecystitis with fibrosis was produced, decreased the rate of solution. In an effort to determine the essential differences between dog and human bile which would account for the solvent capacity of dog bile, additional studies showed that the greatest difference between human and dog bile was in the ratio of the nonsaponifiable (cholesterol) to the saponifiable (fats and fatty acids) substances in the bile. The concentration of saponifiable material in relation to the nonsaponifiable material was found to be relatively low in human bile but very high in dog bile. They concluded that the solubility of cholesterol in bile depends on the activity of the bile salts or bile acids in holding the fats and fatty acids in aqueous solution or in combining with them to form soaps at the acid p_H of the gallbladder.

This report presents additional evidence in support of this hypothesis. We have of necessity repeated a considerable amount of the work reported by Walsh and Ivy but have extended it, using improved methods in an effort to clarify the problem further.

In a previous study we [7] reported the results of treatment in 65 cases of chronic cholecystitis with and without calculi by measures which were designed to increase the free flow of bile. Marked subjective improvement was observed in those patients who received frequent feedings of milk and cream up to the point of tolerance to induce physiologically the contraction and evacuation of the gallbladder and

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mann, D.: Die Lösungsmöglichkeit der Gallensteine, Virchows Arch. f. path. Anat. **212**:139, 1913. Leon, H.: Die gallensteinlösende Wirkung des Karlsbaderwassers, Deutsche med. Wchnschr. **40**:786, 1914. Glaessner, K.: Ueber die Resorption der Gallensteine, Wien. klin. Wchnschr. **31**:549, 1918. Wilhelm, R.: Zur Lösungsvermögung der Galle gegenüber Cholesterensteinen, ibid. **31**:696, 1918. Harrison, F. M., and Barber, W. H.: Effect of Living Gallbladder on Human Biliary Calculi, Proc. Soc. Exper. Biol. & Med. **25**:226, 1927. Mirolli, A.: La ipertrofia e la iperplasia della tonaca muscolare della coleciste nelle colecistiti, Arch. ital. di chir. **30**:314, 1931.

6. Walsh, E. L., and Ivy, A. C.: Observations on the Etiology of Gallstones, Ann. Int. Med. **4**:134, 1930.

7. Brown, C. F. G., and Dolkart, R. E.: Ketocholanic Acids in the Medical Management of Low Grade Gallbladder Disease, J. A. M. A. **108**:458 (Feb. 6) 1937.

ketocholanic acids to stimulate directly the flow of hepatic bile, together with antispasmodic medication to decrease the hypertonicity of the biliary and gastro-intestinal tracts which generally accompanies cholecystitis. Concomitant with the relief of the subjective manifestations of the disease, definite roentgenologic improvement of the function of the gallbladder was noted in a large percentage of cases. Since the first report, 55 additional patients have been given this form of treatment.[8] The results for this group confirm our previous findings.

In view of the clinical improvement in patients with disease of the gallbladder noted with medical management to prevent biliary stasis and to promote emptying of the biliary passages, it was desired to determine the exact extent of the increase in bile flow obtained by the oral administration of oxidized bile acids.

TABLE 1.—*Choleretic Action of Mixed Ketocholanic Acids on Oral Administration to Dogs with a Chronic Biliary Fistula* *

	Control Period		Test Period		
Experiment Number	Days	Average Daily Output of Bile, Cc.	Days	Average Daily Output of Bile, Cc.	Percentage of Increase
1	4	86	4	109	26.7
2	6	100	5	142	42.0
3	4	57	4	80	40.3
4	5	93	11	104	11.8
5	4	81	4	119	46.9
6†	14	408	6	487	19.3

* The dose was 22.5 grains (1.5 Gm.) per day.

† In experiments 1 to 5 the animals were sham-feeding dogs with a biliary fistula, prepared according to the method of Kocour and Ivy. Dog 6 was prepared by the same method but was not a sham-feeding dog. It differed from the 5 others, however, in that it was maintained with constant suction on the tube in the common bile duct. All the dogs had a constant intake of food and fluid during the control and test periods. Bile was returned to each of the animals through a tube into the jejunum in constant amount during the control and test periods.

For this purpose dogs with biliary fistulas were prepared,[9] a modified Rous-McMaster procedure being used after the gallbladder had been removed. In order to maintain the animals in as normal a physiologic state as possible, provision to return part of the bile collected through the fistula was made by the insertion of a catheter into the jejunum. Four dogs with a chronic bilary fistula were used in the experiments. The results are shown in table 1. All the animals were maintained on a constant intake of food and fluid during the periods of observation. The amount of bile returned during the control and test periods was constant for all the animals. In experiment 6 constant suction was maintained in the tube leading into the common duct during the control and test periods, after the method described by Kocour and Ivy.[10]

8. Mock, H. E.; Brown, C. F. G., and Dolkart, R. E.: The Conservative Treatment of Gallbladder Disease, Surg., Gynec. & Obst. **66**:79, 1938.

9. Dr. E. J. Kocour prepared these dogs, and F. W. Gorham assisted with the experiments.

10. Kocour, E. J., and Ivy, A. C.: To be published; personal communication to the authors.

The intravenous action of oxidized bile acids has been studied by numerous investigators,[11] but there have been few reports of the degree of choleresis which is obtained with oral administration. It was observed that the oral administration of oxidized or ketobile acids [12] produced consistent choleresis, increasing the bile flow from 11.8 to 46.9 per cent. The intravenous action of mixed oxidized bile acids (3,7,12-triketocholanic, 3,7-diketocholanic, 3,12-diketocholanic and 3-ketocholanic acid) was found to be more marked, as would be expected. Injection of 7 to 50 mg. per kilogram of body weight to dogs with an acute biliary fistula was found to increase the bile flow from 53.5 to 278.1 per cent. Injection of 250 mg. per kilogram of body weight resulted in an increase of 457.6 per cent in the bile flow.

In view of previous observations of the dissolution of the human gallstone when placed in the gallbladder of the dog, we wished to determine next whether the normal rate of dissolution in the dog could be altered by placing the animal on a regimen to increase the flow of bile similar to that received by the series of patients under our observation.

Through an abdominal incision a stab wound was made in the fundus of the gallbladder after aspiration of the bile contained therein. A human gallstone, that had been weighed, was then inserted, and the opening was closed with a purse string suture. After an interval of sixty-five days each dog was killed, the cystic duct was ligated and the gallbladder was removed. The stones or fragments thereof were again weighed, and the loss of weight was determined. Eighty-eight dogs were used in the experiments, 76 of which survived the duration of the sixty-five day period of observation. For statistical and comparative purposes the animals were divided into three groups. For the first series of animals (14 controls and 20 treated animals) a miscellaneous assortment of gallstones obtained from the gallbladders of various human beings was used. For the second group of animals (10 controls and 21 treated animals) human gallstones were used which were obtained from one gallbladder. For the 11 animals in group 3, stones obtained from one gallbladder were used. In groups 2 and 3 we attempted to eliminate from the experiment the variable due to differences in gallstones obtained from different gallbladders, assuming that stones obtained from one gallbladder are of similar character. Table 2 shows the results of these experiments.

It will be observed that in the first group of animals, in which miscellaneous stones were used (group 1, A and B), a considerable increase in the rate of dissolution occurred in the dogs which received ketocholanic acids to increase the biliary flow. When we attempted to repeat this experiment under conditions that were better controlled, that is, by

11. Neubauer, E.: Dehydrocholsäure, eine wirksaures ungiftiges Glied der Gallensäuregruppe, Klin. Wchnschr. **2**:1065, 1923. Adler, A., and Schmid, E.: Diagnostische und therapeutische Verwendbarkeit der Gallenssäures der Leber und Gallenblase, Fortschr. d. Therap. **1**:733, 1925.

12. Ketochol was used, being supplied by G. D. Searle & Co., Chicago.

elimination of the variable due to the use of miscellaneous stones (group 2, A and B), we were unable to confirm our previous results.

However, the material used in these two sets of experiments differed, in that that used in the second set had been further processed and purified and a residue of impure material had been removed. When the second set of experiments (group 2, A and B), in which stones from one gallbladder were used, failed to confirm the original findings, it was at first thought possible that the change in the purity of the ketocholanic acids might have had some bearing on the results. In an effort to check this possibility an additional group of animals (group

TABLE 2.—*Composite Table of the Results of Solution of Human Gallstones in the Gallbladder of the Dog* *

Type of Stone	Number of Dogs	Treatment	Average Original Weight, Gm.	Average Final Weight, Gm.	Average Loss of Weight, Gm.	Average Loss, %	Probable Error
Group 1							
A. Misc.	14	Controls, given stock diet only	0.316	0.095	0.209	73.3	±5.610
B. Misc.	20	Stock diet plus 22.5 grains (1.5 Gm.) of ketocholanic acid daily	0.281	0.008	0.278	98.0	±0.014
Group 2							
A. MR1	10	Controls, given stock diet only	0.486	0.075	0.410	83.7	±2.330
B. MR1	10	Stock diet plus 22.5 grains (1.5 Gm.) of ketocholanic acid daily	0.488	0.086	0.402	83.5	±2.540
C. MR1	6	Stock diet plus 33.75 grains (2.2 Gm.) of ketocholanic acid daily	0.355	0.061	0.311	82.9	±4.030
D. MR1	5	Stock diet plus 30 grains (2 Gm.) of ketocholanic acid residue daily	0.325	0.028	0.297	91.3	±1.960
Group 3							
A. W	6	Controls, given stock diet only	0.426	0.078	0.354	83.6	±5.190
B. W	5	Diet: high unsaturated fat 3 times daily; high in protein; high in tryptophan; plus 33.75 grains (2.2 Gm.) of ketocholanic acid daily	0.323	0.006	0.317	98.5	±0.607

* The duration of the period of observation was sixty-five days.

2, C) were given a sample of unpurified ketocholanic acids prepared exactly as for the animals in group 1. In addition, another group of 5 animals (group 2, D) were given an equivalent quantity of the impure residue in place of the ketocholanic acids. It will be observed that in no instance was there any significant alteration from the normal rate of dissolution.

With the third group of animals we made an effort to bring about the interaction of several factors, all of which should theoretically have a definite effect in influencing the rate of dissolution of the gallstones. The first factor in the therapy was designed to increase the flow of bile. For this purpose the animals received linseed oil three times daily, because of the well established observations that fat in the duodenum causes evacuation of the gallbladder. Linseed oil was chosen because

the effect of an unsaturated fat was desired. In addition, the animals received ketocholanic acids by mouth to stimulate the increased production of bile by the liver.

The second factor in the therapy was an effort to increase the production of bile salts by bringing certain metabolic factors into play. Whipple and his co-workers [13] have shown that in dogs the output of bile salt is fairly constant with uniform dietary conditions. Fasting was found to reduce the output of bile salts to low levels. Smith and Whipple [14] in further studies demonstrated that meat or meat products fed to dogs with a biliary fistula resulted in an increased production of whole bile and a twofold to threefold increase in the output of bile salts. In attempting to ascertain the essential factor in food protein, further feeding experiments were carried out, gelatin being used as the basic protein.[15] They found that gelatin feeding supplemented by the addition of tryptophan produced a sustained rise in the output of bile salts.

The animals of group 3 in our experiments were given, therefore, in addition to a regimen to increase the flow of bile, a diet which was high in protein and high in tryptophan in an effort to increase the production of bile salts, as suggested by Whipple. Although the table shows there was an increase of approximately 15 per cent in the rate of dissolution of the stones in the treated dogs, we do not consider this to be statistically significant in view of the probable error of the experiment. Three of the control dogs showed 90 per cent or greater dissolution, and the remaining 3 controls brought the average down to 83.6 per cent.

These results show that no significant difference could be demonstrated in the rate with which dogs normally dissolve human gallstones, despite several variations in therapy. Our findings are much in agreement with those reported by Walsh and Ivy, although they suggest that slightly increased dissolution was obtained by the addition of bile salts and cod liver oil to the diet. Two possible conclusions may be drawn: First, either the therapy was ineffective in achieving any significant alteration of the constituents of the bile or an increase of the flow of bile is not a pertinent factor to increasing the rate of dissolution. The second possible conclusion is that in the normal dog the bile in the gallbladder is of such solvent character that it works at optimum capacity and is

13. Smith, D. P.; Groth, A. H., and Whipple, G. H.: Bile Salt Metabolism: I. Control Diets, Methods, and Fasting Output, J. Biol. Chem. **80**:659, 1928.

14. Smith, H. P., and Whipple, G. H.: Bile Salt Metabolism: II. Influence of Meat and Meat Extractives, Liver and Kidney, Egg Yolk and Yeast in the Diet, J. Biol. Chem. **80**:671, 1928.

15. Whipple, G. H., and Smith, H. P.: Bile Salt Metabolism: III. Tryptophane, Tyrosine, and Related Substances as Influencing Bile Salt Output, J. Biol. Chem. **80**:685, 1928.

consequently not affected by therapy. In the light of the studies of Walsh and Ivy, we believed the latter to be more probable.

We wished to determine next whether there is any essential difference in the stone-solvent properties of the bile in the gallbladder of the group of animals which form gallstones spontaneously and of animals in which they do not occur. If there was a difference in stone-solvent properties of the bile of these animals, we wished to determine which fraction of the bile was responsible and whether this could be correlated in any way with the great solvent capacity of dog bile.

The first factor to be studied in this connection was the role of the p_H of the bile. To carry on these investigations we performed in vitro experiments, using in general the procedure described by Walsh and Ivy.

Human gallstones, similar in character and obtained from one gallbladder, were weighed, wrapped in gauze to prevent mechanical injury and suspended in flasks to which was added either acid or alkaline bile. These flasks were then placed in a mechanical shaking device operating at a speed of 25 to 30 half revolutions per minute. The stones were shaken continuously for seven days in a constant temperature chamber at 39 C. Seventy experiments were carried out with human, dog and ox bile which had been buffered to maintain a p_H of 4.5 to 5 for half of the experiments and a p_H of 8.4 to 9 for the other half. Other studies were carried out in which the p_H of the bile in the gallbladder of the dog was measured at the time of the insertion of a human gallstone and sixty-five days later, when the stone was removed.

No statistically significant difference was observed in the relative solvent action of acid and of alkaline bile from the ox, the dog and man on human gallstones of the mixed cholesterol variety.[16] These findings were not in agreement with the conclusions drawn by Feldman, Morrison and Krantz from their observations that the human gallstone dissolved in the gallbladder of the dog, which was an acid bile, but did not dissolve in the gallbladder of the guinea pig, which has an alkaline bile.[17] They concluded that the p_H of the bile is the important factor in determining whether or not a human gallstone will dissolve in an animal's gallbladder. On the basis of our studies and the examination of their data, we believe their conclusions to be unwarranted.

Other experiments were carried out in vitro by the technic described, in which solutions of bile salts were used as the mediums in which the gallstones were shaken. Table 3 shows the results of these miscellaneous experiments. In the course of these studies in shaking human gallstones, it was observed that there were certain experimental diffi-

16. Dolkart, R. E.; Jones, K. K., and Brown, C. F. G.: The Relation of the Hydrogen Ion Concentration of Bile to the Formation of Gallstones, Am. J. Digest. Dis. & Nutrition **4**:587, 1937.

17. Feldman, M.; Morrison, S., and Krantz, J. C.: Etiology of Gallstones, Am. J. Digest. Dis. & Nutrition **4**:13, 1937.

culties. In the first place, it was difficult to obtain a sufficient number of human gallstones from one gallbladder to make an adequate number of comparative experiments. In the second place, there was considerable variation in the size and in the weight of the stones obtained from the same gallbladder, so that there was no constancy of surface area in contact with the dissolving solution. In the third place, it was believed that even though stones were obtained from the same human gallbladder there was no assurance that they were of exactly the same composition, in which case the number of experimental variables would be further increased. To overcome these difficulties, four thousand human gall-

TABLE 3.—*Composite Table of Results of Shaking Human Gallstones in Vitro at 39 C. at Twenty-Five to Thirty Half Revolutions per Minute for Seven Days* *

Solution Used	Stones A		Stones B		Stones C		Stones D	
	No. of Exper.	Loss of Weight, %	No. of Exper.	Loss of Weight, %	No. of Exper.	Loss of Weight, %	No. of Exper.	Loss of Weight, %
1% solution of sodium glycocholate in 5% sodium carbonate	17	−4.34 ± 0.985	25	−5.52 ± 0.177	..	.....	12	−5.20 ± 0.395
1% solution of sodium salts of mixed ketocholanic acids, p_H 8.3	24	−2.01 ± 0.553	10	−2.67 ± 0.072	20	−3.82 ± 0.728	8	−2.88 ± 1.605
1% solution of mixed ketocholanic acids in 5% sodium carbonate	30	−7.67 ± 0.072	30	−2.91 ± 0.170	16	−3.45 ± 0.480	4	−3.80 ± 0.548
1% solution of bile salts; fatty acid residue †	12	−2.73 ± 0.140	10	−0.72 ± 0.083	..	.....	8	−1.84 ± 1.221
1% solution of iron bile salts, mixture	5	−11.29 ± 0.799	5	−6.15 ± 0.219	..	.....	..	.....
Distilled water, control	12	−0.20 ± 0.096	10	−0.73 ± 0.066	..	.....	12	−0.51 ± 0.609

* The gallbladders from which the stones were obtained are designated by letters A, B, C and D.

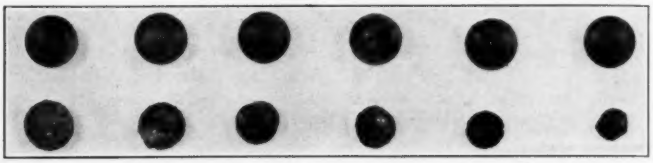
† See the discussion of the methods and materials.

stones of mixed variety were collected. These stones had been removed either at operation or at autopsy, and were prepared as follows:

The stones were pulverized, the powder was thoroughly mixed and the material was run through a pharmaceutic tablet press under considerable pressure. It was found that the pulverized material had adequate cohesive power, and the addition of starch or other binders was unnecessary. The gallstone tablets thus obtained were of uniform size, density and composition. The variations in weight between a large number of tablets was extremely small. Analysis of the tablets showed them to contain 70.6 per cent cholesterol. Eighteen hundred and forty comparative experiments were performed with the standardized gallstone tablets prepared by this method. Twenty tablets were shaken separately in each of the solutions indicated in the accompanying tables, the average loss of weight was determined and the probable error was computed. The accompanying figure shows the tablets which were not shaken as compared with tablets in various stages of dissolution after shaking.

Owing to the fact that the gallstone tablets were prepared from the mixed variety of human gallstones, it would be theoretically possible for the various solutions employed to dissolve out the noncholesterol components. We checked this factor by determining the cholesterol content of the tablets and by comparing these figures with those obtained for tablets which were not shaken. The results showed that most of the losses in weight in each case could be accounted for by the decrease in the cholesterol content. The question may well arise at this point as to whether the cholesterol actually went into solution or whether it was merely dispersed in the shaking solutions. From our data it appears that the former was the case. We are, however, studying this phenomenon further in another group of experiments.

In attempting to determine the factors concerned in the dissolution of cholesterol gallstones in animal bile, the bile obtained from the ox and the hog, animals which form gallstones, was compared with the bile obtained from the sheep and the dog, animals which do not form gallstones. Table 4 shows that undiluted bile from the gallbladder of each of



The top row of gallstone tablets have not been shaken. The bottom row of tablets have been shaken and dried and are in various stages of dissolution.

these animals had a definite solvent capacity under the uniform conditions of the experiments. Dilution with distilled water resulted either in a total loss or in a marked reduction of the solvent power. A fresh portion of the bile from each of these animals was then extracted with an equal volume of 95 per cent alcohol, which separated it into two fractions. The alcohol-insoluble fraction was filtered out, the alcohol evaporated off and the residuum taken up in distilled water in the concentrations indicated in the table. In no instance did the alcohol-insoluble fraction, consisting chiefly of protein, mucin and inorganic salts, manifest any significant dissolving power.

Shaking experiments were next carried out, the alcohol-soluble fractions being used as the shaking mediums. Before the stones were shaken in these fractions, the alcohol was evaporated off, and by the addition of distilled water, the remaining alcohol-soluble material was brought to a concentration equivalent to that in which it occurred in the bile. Stones shaken in this fraction showed considerable dissolution. In some instances this was either equal to or greater than the dissolution

occurring in the undiluted whole bile. When the alcohol-soluble fraction was saponified, two more bile fractions were obtained. The nonsaponifiable fraction, consisting of approximately 80 per cent cholesterol, was found to be so highly insoluble that it could not be used as a meduim in which to carry out shaking experiments. When stones were shaken in the saponifiable or fatty acid fraction, however, the solvent power was found to be either quantitatively equal to or greater than that of undiluted bile.

On the basis of these findings it appears that the solvent capacity of bile can be isolated in the saponifiable or fatty acid fraction. We wished to determine next whether there was any correlation between the

TABLE 4.—*Dissolution of Standardized Gallstone Tablets Made from Human Gallstones in Various Fractions of Animal Bile* *

Bile Fraction	Ox Gallbladder Bile, %	Hog Gallbladder Bile, %	Sheep Gallbladder Bile, %	Dog Gallbladder Bile, %
Undiluted bile	−7.50 ± 0.371	−7.87 ± 0.133	−5.29 ± 0.467	−11.20 ± 0.143
Bile diluted 1:5 with distilled water	−0.07 ± 0.094	−4.24 ± 0.105	−2.82 ± 0.368	
Bile diluted 1:10 with distilled water	−0.07 ± 0.145	−2.75 ± 0.095	−2.30 ± 0.152	
Alcohol-insoluble fraction, equivalent to normal concentration	+0.81 ± 0.320	−1.48 ± 0.068	−0.26 ± 0.168	−3.30 ± 0.212
Alcohol-insoluble fraction, concentrated 5 times	−1.20 ± 0.341	−3.68 ± 0.155	−2.14 ± 0.200	
Alcohol-soluble fraction, equivalent to normal concentration	−4.87 ± 0.209	−8.79 ± 0.324	−8.79 ± 0.525	
Alcohol-soluble saponifiable fraction, equivalent to normal concentration	−7.17 ± 0.276	−12.41 ± 0.302	−9.30 ± 0.196	−15.20 ± 0.254

* Each figure represents the average percentage of loss of weight for twenty experiments made simultaneously, with the probable errors determined. All the experiments show the result of one week of shaking at 25 to 30 half revolutions per minute at 39 C.

relative amounts of saponifiable material present in the bile of these animals. Table 5 shows the result of the analyses performed on samples of the animal biles used in the shaking experiments. It will be observed that the relative ratio of saponifiable to nonsaponifiable material was very high for the dog and the sheep but low for the ox and the hog. Other analyses of bile from human gallbladders showed that this ratio was even lower (1.5 : 1) than that found for these two species of stone-forming domestic animals.

In view of these observations, confirming the findings of Walsh and Ivy and of the numerous reports in the literature which ascribe the chief role in maintaining cholesterol in solution to the bile salts and bile acids, an additional group of shaking experiments were made in which the relative solvent action of various bile salts could be compared with that of fatty acids on an equitable basis. These results are shown in table 6 and will be discussed further. It should be noted at this point,

however, that in no instance did the solvent action of any of the bile salts approach that of any of the fatty acids used in the experiments.

TABLE 5.—*Quantitative Analyses of Animal Biles* Used for Fractionating Experiments†*

Determination	Ox Gallbladder Bile, Gm. per 10 Cc.	Hog Gallbladder Bile, Gm. per 10 Cc.	Sheep Gallbladder Bile, Gm. per 10 Cc.	Dog Gallbladder Bile, Gm. per 10 Cc.
Total solids	1.2760	1.5600	1.2490	2.5520
Total ash	0.1335	0.0790	0.1120	0.0976
Alcohol-insoluble material	0.0350	0.1798	0.0870	0.1930
Nonsaponifiable fraction	0.0100	0.0190	0.0060	0.0142
Cholesterol	0.0060	0.0100	0.0045	0.0113
Saponifiable fraction	0.0630	0.1080	0.0778	0.2850
Bile salts, determined as cholic acid‡	.....	0.0600	0.3100	1.1500
Ratio: saponifiable to nonsaponifiable fraction	6.3:1	5.6:1	12.9:1	20.3:1

* All the samples were of summer bile. The analyses for ox bile were made on an aliquot sample from 5 gallons of fresh beef bile obtained from the stockyards. The analyses for hog bile were made on an aliquot sample from 3 gallons of fresh hog bile obtained from the stockyards. The analyses for sheep bile were made on an aliquot sample of 2 gallons of fresh sheep bile obtained from the stockyards. At 30 cc. of bile per sheep, which is the average content of the sheep gallbladder, this represents the bile of 253 sheep. The dog bile was obtained from a large number of laboratory animals.

† All the figures represent analyses of 10 cc. samples, with all determinations in duplicate.

‡ Method of Reinhold and Wilson (J. Biol. Chem. **96**: 637, 1932).

TABLE 6.—*Dissolution of Standardized Gallstone Tablets Made from Human Gallstones in Various Solutions of Bile Salts and Fatty Acids**

Solution	Percentage with 1% Concentration	Percentage with 5% Concentration	Percentage with 10% Concentration
Sodium glycocholate	− 2.99 ± 0.074	− 9.60 ± 0.341	−17.50 ± 0.415
Sodium taurocholate	− 3.90 ± 0.138	−12.30 ± 0.246	−22.30 ± 0.419
Sodium cholate	− 5.10 ± 0.110	−19.90 ± 0.482	−34.50 ± 0.526
Sodium desoxycholate	− 2.80 ± 0.071	−19.10 ± 0.488	−18.60 ± 0.381
Mixed bile salts (Wilson)	− 4.90 ± 0.154	− 7.71 ± 0.147	−15.70 ± 0.890
Bile salts mixture with iron (Lilly)	− 4.10 ± 0.098	− 5.20 ± 0.119	− 8.30 ± 0.219
Sodium dehydrocholate (sodium salt of 3, 7, 12-triketocholanic acid)	− 0.34 ± 0.040	− 1.47 ± 0.097	− 2.69 ± 0.094
Sodium dehycrodesoxycholate (sodium salt of 3, 12-diketocholanic acid)	− 2.18 ± 0.067	− 3.69 ± 0.127	− 4.99 ± 0.148
Mixed ketocholanic acids (Searle)	− 5.80 ± 0.161	−10.32 ± 0.154	−11.52 ± 0.080
5% sodium carbonate; control	.....	− 0.66 ± 0.305	.....
Sodium linoleate, 39 C.	−11.24 ± 0.283	−16.62 ± 0.460	−20.78 ± 0.473
Sodium oleate, 39 C.	−22.50 ± 0.490	−36.50 ± 0.455	−49.00 ± 0.469
Sodium oleate, 70 C.	−33.80 ± 0.422	−64.60 ± 0.716	−76.50 ± 1.070
Sodium laurate, 70 C.	−52.10 ± 0.325	−97.85 ± 1.082	−100.00 ± 0.000
Sodium stearate, 70 C.	−32.40 ± 1.120	−48.60 ± 1.310	−57.60 ± 1.201
Sodium myristate, 70 C.	−48.60 ± 0.938	−71.10 ± 0.880	.....
Sodium palmitate, 70 C.	−13.10 ± 0.306	−53.40 ± 0.654	−62.20 ± 0.519
Sodium lauryl sulfonate, —39 C.	−27.30 ± 0.269	−31.88 ± 0.796	−32.42 ± 0.451
Lecithin in water, —39 C.	− 1.64 ± 0.077	− 1.06 ± 0.103	.....

* Each figure represents the average percentage of loss of weight in twenty experiments made simultaneously, with the probable errors determined. All the experiments are the results of 1 week of shaking at 25 to 30 half revolutions per minute at 39 C. Some of the experiments were made at a temperature of 70 C. and are so indicated. All bile salts and bile acids were dissolved in a 5 per cent solution of sodium carbonate; fatty acids in sodium hydroxide added in sufficient amount to bring the p_H of the solution to 8.3.

In comparing the relative activity of the various bile salts used, on first inspection it appeared that perhaps the reason sodium cholate

showed the greatest solvent capacity was that the solutions used were prepared as percentage concentrations rather than as molar solutions. Recalculation of the data on the basis of the relative molar concentrations, however, showed that there was no correlation.

Table 7 shows the relative action of the solutions containing both bile salts and fatty acids, each in 5 per cent concentration. It will be

TABLE 7.—*Dissolution of Standardized Gallstone Tablets Made from Human Gallstones in Solutions Containing 5 per Cent Sodium Glycocholate Mixed with 5 per Cent Fatty Acids as Soaps (p_H 8.3)**

Solution	Temperature, C.	Dissolution, %	Percentage of Dissolution, Only the Soap (5%) Being Used	Percentage of Dissolution, Only the Bile Salt (5%) Being Used
Sodium laurate and sodium glycocholate	70	−53.35 ± 0.377	−67.85 ± 1.032	− 9.61 ± 0.182
Sodium palmitate and sodium glycocholate	70	−48.00 ± 0.512	−53.40 ± 0.654	− 9.61 ± 0.182
Sodium stearate and sodium glycocholate	70	−41.92 ± 0.269	−48.60 ± 1.310	− 9.61 ± 0.182
Sodium oleate and sodium glycocholate	70	−56.30 ± 0.809	−64.60 ± 0.716	− 9.61 ± 0.182
Sodium oleate and sodium glycocholate	39	−29.90 ± 0.185	−36.50 ± 0.455	− 9.60 ± 0.341
Sodium linoleate and sodium glycocholate	39	−33.00 ± 0.236	−16.62 ± 0.469	− 9.60 ± 0.341

* Each figure represents the average loss of weight of twenty stones shaken for one week, at 25 to 30 half revolutions per minute, at the temperature indicated.

TABLE 8.—*Correlation of Relative Activity of Fatty Acids as Soaps on Basis of Their Molar Concentrations*

Fatty Acid Soap	Molecular Weight	Melting Point of Fatty Acid, C.	Molar Concentration of 10% Shaking Solution	Percentage of Dissolution in 10% Solution	Ratio of Molar Concentration to Percentage of Dissolution
Sodium laurate	222.19	47-48	0.45	100.0	222
Sodium myristate	250.22	57-58	0.40	100.0*	250*
Sodium palmitate	278.25	63-64	0.36	62.2	172
Sodium stearate	306.28	69-70	0.32	57.6	180
Sodium oleate	304.27	14	0.32	49.0	153
Sodium linoleate	302.25	18	0.32	20.7	64

* Based on the theoretic result, as the stones were not shaken in the 10 per cent concentration. Since 71.1 per cent dissolution occurred in 5 per cent solution it is assumed that the stones would have entirely dissolved in the 10 per cent solution.

observed that the solvent capacities of the solutions were analogous to the order of activity of the fatty acids as soaps alone, but, contrary to expectations, they were not as great except in the case of sodium linoleate. This finding further supports the hypothesis that the fatty acids in bile are more concerned with maintaining the cholesterol in solution than are the bile salts, even though in normal animal bile the concentration of the fatty acids is much lower than the concentrations used in some of the shaking experiments.

In table 8 we attempted to correlate the relative activity of the various fatty acids as soaps on the basis of their molar concentrations. It will be seen, as in the case of the bile salts, that there was no correlation—indicating that the solvent activity was chiefly a chemical phenomenon. It is interesting to note that there is apparently an optimal length to the chain of carbon atoms. For example, the short chain fatty acids, such as lauric acid, are highly active as cholesterol solvents. Fatty acids with fewer carbon atoms than lauric acid, such as caprylic and butyric acid, are practically inert.

All these results indicate the importance of the fatty acids as cholesterol solvents. In other experiments we have observed that when gallstones are placed in liquid fatty acids they soon disintegrate, all the cholesterol going into solution. We believe that the solvent action of the fatty acids in bile depends on the amount of fatty acids that may be held in a watery menstruum. The fatty acids themselves are quite insoluble in water, but in alkaline solution as soaps they are decidedly more soluble. At an acid reaction the fatty acids are precipitated unless they are in a solution with a markedly reduced surface tension. In this latter function the bile salts are effective. Taurine, like all sulfonic acids, is especially effective in lowering the surface tension.

Lauric acid, of all the fatty acids, is best able to resist precipitation by electrolytes. Its ability to remain in solution in the presence of sodium chloride makes it useful as a marine soap. Sodium laurate is able to maintain a definite solution at a p_H of 6 to 7. It is not surprising, in the light of this, that Walsh and Ivy found lauric acid to be the most effective fatty acid in dissolving gallstones—a fact that we have completely confirmed.

The line seems clearly drawn that bile may be divided into a gallstone-forming component and a gallstone-dissolving component. These may be roughly represented by the saponifiable and the nonsaponifiable fraction in the bile. Searing and one of us (K. K. J.)[18] have shown that diet has a small but definite effect in changing the ratio of saponifiable to nonsaponifiable material in the hepatic bile of the dog, an effect which is probably even greater in human beings, as suggested by our clinical studies.[19] In the experiments on dogs a milk diet proved the most effective in increasing the fatty acid fraction. This is even more interesting when it is recalled that milk fat has a relatively high lauric acid content.

18. Jones, K. K., and Searing, E. A.: The Saponifiable and Non-Saponifiable Matter in Bile as Affected by Diet, Am. J. Physiol. **116**:87, 1936.

19. Brown and Dolkart.[7] Mock, Brown and Dolkart.[8]

COMMENT

Efforts to correlate the type of bile acids common to a species of animals with dietary and metabolic factors have thus far been unsuccessful. Cholic acid appears to be common to all animals with the exception of guinea pigs, rabbits and certain rodents, according to Sobotka and others. Human, dog, ox, sheep and hog bile have been shown by numerous workers [20] to yield a mixture of cholic, desoxycholic, chenodesoxycholic and lithocholic acids on alkaline hydrolysis. Hog bile, in addition, has been shown to contain hyodesoxycholic acid.[21] These bile acids are thought to occur in the bile in peptide-like conjugation, with aminoacetic acid and taurine as the water-soluble sodium salts.[22] In man, the ox and the hog the glyco acids are more abundant, whereas in the dog the tauro acids predominate. These bile salts function chiefly in the process of digestion and absorption, where they act to maintain the water-soluble fats and cholesterol in solution or dispersion. It is still unknown whether they act in this regard as emulsifying agents only or whether they form water-soluble molecular compounds with the fats.

Wieland and Sorge [23] have reported the occurrence of a substance known as choleic acid which is water soluble and which was formerly considered a true bile acid, but which was actually found to be a coordinated compound containing one molecule of fatty acid and eight molecules of desoxycholic acid. They then suggested that the dissolving power of bile is due to the choleic acid principle. Fieser [24] has stated that he does not agree with this hypothesis, on the grounds that desoxycholic acid is not the most abundant of the bile acids obtained from bile and the other bile acids do not have the property of forming choleic acids. A second objection, voiced by Sekitoo,[25] is that desoxycholic acid does not occur free as such in bile but occurs in conjugation with aminoacetic acid and taurine, in which form it is questionable whether

20. Wieland, H., and Weyland, P.: Untersuchungen über die Gallensäuren: VIII. Zur Kenntnis der Lithocholsäure, Ztschr. f. physiol. Chem. **110**:123, 1920. Okamura, S., and Okamura, T.: Ueber die Gallensäure der Kaninchengalle, ibid. **188**:11, 1930. Windaus, A.; Bohne, A., and Schwarzkopf, E.: Ueber die Cheno-desoxy-cholsäure, ibid. **140**:177, 1924.

21. Windaus, A., and Bohne, A.: Ueber Hyo-glyko-desoxy-Cholsäure und über Hyo-desoxy-Cholsäure, Ann. d. Chem. **433**:278, 1923.

22. Fieser, L. F.: The Chemistry of Natural Products Related to Phenanthrene, New York, Reinhold Publishing Corporation, 1936, p. 123.

23. Wieland, H., and Sorge, H.: Untersuchungen über die Gallensäuren: II., Ztschr. f. physiol. Chem. **97**:1, 1916.

24. Fieser,[22] p. 131.

25. Sekitoo, T.: Beiträge zur Kenntnis der Glykocholeinsäure aus Kaninchengalle, Ztschr. f. physiol. Chem. **199**:225, 1931.

the other bile acids could form compounds of stability with fatty acids which are comparable to the desoxycholic acid compounds.

Verzár,[26] on the other hand, has shown that combinations of bile acids and fatty acids do occur in the intestinal canal. His observations have shown that combinations of desoxycholic acid and cholic acid with fatty acids are stable only in an alkaline medium down to p_H 7.1 to 7.9 and are unstable at an acid reaction of p_H 6 to 7. Combinations of sodium taurocholate and glycocholate are stable up to an acid reaction of p_H 5.9 to 6.1. He therefore has stated that he considers the taurocholates and the glycocholates of greater importance in the intestinal canal because they form water-soluble diffusible combinations which are stable in the physiologic p_H range of the intestine, which is slightly acid. While Verzár's observations on the relative importance of the various bile acids in the intestine and their activity in combinations with fatty acids do not necessarily hold for their importance in the biliary tract, they are of interest because they establish certain factors in the interrelation of the bile acids and the fatty acids.

The mechanisms whereby the cholic and other bile acids are conjugated in the animal body with taurine and aminoacetic acid are thought to be intimately associated with hepatic function. In the presence of hepatic disease, incomplete conjugation may occur, or free bile acids may be secreted,[27] Whipple [28] and Walters [29] have shown that small degrees of hepatic damage, subclinical as far as symptoms are concerned, result in a marked decrease in the bile salt content of the bile. Walters, Greene and Fredrickson [30] have reported that after relief of obstructive jaundice, a diminuation in the excretion of bile salts is observed, which later returns to normal.

Andrews and his co-workers [31] have hypothesized that gallstones form as the result of abnormalities of bile salt metabolism, occurring either primarily in the liver or as the result of an abnormal diffusion of the bile salts out of the gallbladder, allowing the cholesterol which is held in solution by the bile salts to precipitate out and form stones. They concluded that the significant factor to be considered in the forma-

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26. Verzár, F., and McDougall, E. J.: Absorption from the Intestine, London, Longmans, Green & Co., 1936, p. 163.

27. Sobotka, H.: Physiological Chemistry of the Bile, Baltimore, Williams & Wilkins Company, 1937, p. 29.

28. Whipple, G. H.: Bile Salt Metabolism, J. Biol. Chem. **59**:623, 1924.

29. Walters, W.: Obstructive Jaundice: Physiologic and Surgical Aspects, Rochester, Minn., Mayo Foundation, 1931.

30. Walters, W.; Greene, C. H., and Fredrickson, C. H.: Composition of Bile Following the Relief of Biliary Obstruction, Ann. Surg. **91**:686, 1931.

31. Andrews, E.; Hrdina, L., and Dostal, L. E.: Etiology of Gallstones: II. Analysis of Duct Bile from Diseased Livers, Arch. Surg. **25**:1081 (Dec.) 1932.

tion of gallstones is the relative ratio of the bile salts to the cholesterol content of the bile. They further stated that on the basis of their studies it seems that there is no substance other than bile salts in the bile capable of holding cholesterol in solution.[32]

Reinhold, Ferguson and Hunsberger[33] have reported that in the presence of disease of the gallbladder the concentration of cholic acid was found to be significantly diminished from the normal level in bile from the gallbladder. This was attributed to increased permeability of the mucosa of the diseased gallbladder to bile salts, as suggested by Andrews and his group. These authors also expressed the opinion that in the presence of injury to the hepatic parenchyma or of obstruction of the bile ducts, alteration or suppression of the secretion of bile acid may be additional factors, on the basis of studies by Doubilet;[34] Riegel, Ravdin, Morrison and Potter;[35] McMaster, Broun and Rous;[36] Goff, Hrdina and Andrews,[37] and others.

The studies of Walsh and Ivy were the first to indicate that the role of the bile salts in maintaining cholesterol in solution is chiefly secondary to the role played by the fatty acids. Our results confirmed these findings. Using more accurate analytic methods than those employed by these investigators and making a greater number of experiments, we have obtained several interesting differences in results. Of all the various bile salt preparations used in the experiments, the sodium salt of pure cholic acid proved to have the greatest cholesterol-solvent capacity, with sodium taurocholate, sodium desoxycholate and sodium glycocholate, in the order named, next in activity. There appears to be an optimum concentration for some of the preparations used. Our results are not in agreement with those reported by Rosin[38] in the laboratories of

32. Andrews, E.; Dostal, L. E., and Hrdina, L.: Etiology of Gallstones: IV. Is Cholesterol Excreted by the Gallbladder Mucosa? Arch. Surg. **26**:382 (March) 1933.

33. Reinhold, J. G.; Ferguson, L. K., and Hunsberger, A.: The Composition of Human Gallbladder Bile and Its Relationship to Cholelithiasis, J. Clin. Investigation **16**:367, 1937.

34. Doubilet, H.: Differential Quantitative Analysis of Bile Acids in Bile and in Duodenal Drainage, J. Biol. Chem. **114**:289, 1936.

35. Riegel, C.; Ravdin, I. S.; Morrison, P. J., and Potter, M. J.: Studies of Gallbladder Function: XI. The Composition of the Gallbladder in Pregnancy, J. A. M. A. **105**:1343 (Oct. 26) 1935.

36. McMaster, P. O.; Broun, G. O., and Rous, P.: Studies on the Total Bile: III. On the Bile Changes Caused by a Pressure Obstacle to Secretion and on Hydrohepatosis, J. Exper. Med. **37**:685, 1923.

37. Goff, M.; Hrdina, L., and Andrews, E.: Effect of Prolonged Stasis on the Bile Salt-Cholesterol Ratio, Proc. Soc. Exper. Biol. & Med. **29**:549, 1932.

38. Rosin, A.: Ueber die Lösung von Gallensteinen, Ztschr. f. physiol. Chem. **124**:282, 1923.

Aschoff and Wieland. She compared the dissolving effect of individual bile acids on cholesterol and pigment gallstones and found desoxycholic acid the most efficient. Next in order of activity were glycocholic, cholic and taurocholic acid. Her results, however, were based on an extremely small number of experiments.

It is interesting to note that changes in the structure of the bile acid molecule have a marked effect on the ability of the particular acid to hold cholesterol in solution. Conjugation with aminoacetic acid or taurine somewhat decreases this ability. When cholic acid is oxidized to the dehydro or keto form, the solvent capacity is apparently lost. Sodium dehydrocholate was practically inert in all concentrations. Similarly, the oxidation of desoxycholic acid to the keto form resulted in a marked loss of solvent capacity. In view of the fact that the preparation of mixed ketocholanic acid used showed moderate ability to hold cholesterol in solution, it appears that some additional substance—possibly chenodesoxycholic or lithocholic acid—is present. No color reaction, however, is obtained when the Reinhold and Wilson modification of the Gregory-Pascoe method for determining cholates is used on the preparation of mixed ketocholanic acids employed in the experiments.

On the basis that bile salts are of chief importance in maintaining cholesterol in solution in bile, thus preventing the formation of gallstones, much research has been carried out in an effort to bring about significant increases in the production of bile salts. Sobotka [39] has stated the opinion that such studies are unsatisfactory at present because analytic procedures determine the concentration of only cholic acid. Experimental increases or decreases in total bile acids cannot be interpreted properly, according to this author, because cholic acid may decrease in favor of desoxycholic acid, chenodesoxycholic acid, keto acids and certain abnormal forms which escape the colorimetric method used. Therefore, much of the investigative work on bile salt determinations reported thus far is subject to serious question on such grounds.

Our results demonstrate that bile salts are not the most essential substances for maintaining cholesterol in solution in the bile. In equivalent concentrations the fatty acids were far more active as cholesterol solvents than were the bile acids. The studies of the cholesterol-solvent capacity of fractions of bile showed that whether or not the animal belonged to a species which forms gallstones, if the bile was solvent for cholesterol, the solvent capacity could be isolated in the saponifiable or fatty acid fraction. In addition to this fact it was observed that there was a considerable decrease in the amount of this saponifiable fraction in relation to the cholesterol content of the bile in those animals which

39. Sobotka,[27] p. 26.

form gallstones, as compared with the amount in those which never form gallstones.

Whether the fatty acids as they occur in the bile function independently in maintaining the nonsaponifiable material in solution in the bile or whether they act in combination with the bile acids, as suggested by Wieland and Sorge and Verzár, cannot at present be determined. Certainly, however, more attention should be given the role of the fatty acids in the production of gallstones.

SUMMARY AND CONCLUSIONS

Ketocholanic acids have a definite measurable effect in producing choleresis when administered by mouth. No toxic effects were observed as far as pathologic changes in the liver or systemic manifestations following prolonged administration to dogs were concerned.

Bile from the gallbladder of the dog is so solvent for human cholesterol gallstones that we were unable to influence the rate at which human gallstones were normally dissolved in the gallbladder of the dog.

By fractionating bile of the dog and of the sheep (animals which do not form gallstones) and of the ox and of the hog (animals which do form gallstones), it was found that the solvent capacity of the bile could be isolated in the saponifiable or fatty acid fraction.

Quantitative analysis of bile from the gallbladder of these animals showed that the saponifiable fraction was relatively high in the dog and in the sheep but low in the ox and in the hog. Similar analysis of human bile showed that the concentration of the saponifiable fraction was extremely low in proportion to the nonsaponifiable or cholesterol fraction. These findings indicate that the fatty acids in the bile play an extremely significant role in maintaining cholesterol in solution and in preventing the formation of gallstones. Our studies indicate further that the action of fatty acids in this connection is much greater than the action of the bile salts or the bile acids. We do not agree that the mechanism whereby cholesterol is held in solution in the bile is chiefly a function of the bile salts.

PRIMARY CARCINOMA OF THE LUNG

A CLINICAL AND PATHOLOGIC STUDY OF ONE HUNDRED CASES

SIMON KOLETSKY, M.D.
CLEVELAND

Recent reports have emphasized the high and apparently increasing incidence of primary carcinoma of the lung.[1] At the Cleveland City Hospital in the eleven year period from 1927 to 1937, inclusive, there were 100 cases in which autopsy was performed, which constitute 1.3 per cent of 7,685 consecutive cases studied post mortem and 9.4 per cent of 1,064 cases of malignant tumor studied post mortem. At autopsy the lung ranked second only to the stomach as the primary site of carcinoma. While such a postmortem incidence obviously does not represent the true morbidity for the entire population, it serves to reflect again the frequency and importance of this tumor.

A summary of the salient gross and microscopic observations in these 100 cases of primary bronchiogenic carcinoma studied post mortem constitutes the substance of this paper. The attempt will be made to correlate the cell type of the tumor with the mode of growth and the dissemination, as well as with the clinical behavior and the prognosis.

HISTOLOGY

This tumor was classified on the basis of histologic character without difficulty, despite pleomorphism of varying degree. In the 100 cases there were 35 small cell carcinomas, 40 squamous cell carcinomas, 22 adenocarcinomas and 3 tumors which were classified as carcinoma simplex.

Thirty-two of the squamous cell carcinomas were either partly or well differentiated and showed keratinization and keratohyaline pearl formation. Although the pearls were inconspicuous or absent in the 8 cases in which there was poor differentiation, the diagnosis was estab-

From the Pathological Laboratory of the Cleveland City Hospital and the Institute of Pathology, Western Reserve University.

1. Weller, C.: Pathology of Primary Carcinoma of the Lung, Arch. Path. **7**:478-519 (March) 1929. Rosahn, P. D.: The Incidence of Primary Carcinoma of the Lung, Am. J. M. Sc. **179**:803-811 (June) 1930. Olson, K. B.: Primary Carcinoma of the Lung, Am. J. Path. **11**:449-468 (May) 1935. Brines, O. A., and Kenning, J. C.: Bronchiogenic Carcinoma, Am. J. Clin. Path. **7**:120-133 (March) 1937.

lished by the demonstration of compact cords of large, flat, polygonal cells of squamous type with vesicular nuclei and well defined cell borders.

The diagnosis of adenocarcinoma was determined by the presence of acini lined with cuboidal or columnar cells. In 14 of the 22 cases the tumor was either partly or well differentiated and presented a fairly uniform microscopic picture. Evidence of mucinous secretion was noted in 3 of these cases. The 8 poorly differentiated adenocarcinomas exhibited a pleomorphic structure, and well formed acini could not be demonstrated in every microscopic section. In some areas the tumor cells appeared in small groups, with no differentiation, or formed atypical alveoli. Many sections showed invasion of blood vessels, with formation of tumor thrombi in the lumens.

The epithelial origin of small cell carcinoma from the mucosal lining of the bronchial tree is now generally accepted.[2] The term small cell is preferable to the terms oat, spindle and round cell, since the latter indicate merely subvarieties based on the shape of the cell and denote no essential differences in structure. The tumor cells are small and grow in loose or compact alveolar nests which are separated by dense bands of connective tissue. Delicate collagenous bundles extend from the main framework between individual groups of cells. Nuclei are characteristically hyperchromatic and rarely reveal a nucleolus; the cytoplasm is scant and has indistinct borders. The spindle and oat cell varieties often show nuclear palisading, especially in perivascular position. Giant cells with overlapping nuclei are common. A tendency to invade the lymphatic system and the veins is characteristic and accounts for the widespread and distant metastases. Within small vessels the tumor cells frequently lose their characteristic configuration and become spherical, thus simulating white blood cells. Morphologic variations are slight. The tumor may, however, resemble a reticulum cell sarcoma closely, but special staining readily demonstrates that the round cell carcinoma produces no intercellular reticulum. Only 2 tumors were of the transitional cell type, showing compact groups of large oval cells with abundant cytoplasm, vesicular nuclei and occasional nucleoli. Both, however, showed areas of typical "small cells." That this gradation is characteristic of the small cell tumor is proved by the fact that in unquestionable cases areas of transitional cell carcinoma could be demonstrated. This suggests that the transitional cell form may represent an earlier phase in the life history of a small cell carcinoma, the later

2. Barnard, W. G.: The Nature of the "Oat-Celled Sarcoma" of the Mediastinum, J. Path. & Bact. **29**:241-244 (July) 1926. Karsner, H. T., and Saphir, O.: Small Cell Carcinomas of the Lung, Am. J. Path. **6**:553-562 (Sept.) 1930. Maxwell, J.: Primary Malignant Intrathoracic Tumors, J. Path. & Bact. **33**:233-249 (April) 1930.

changes in size, shape and staining property of the tumor cells being due to degeneration or differentiation. In a number of the cases histologic comparison of postmortem material with biopsy specimens obtained at operation supported this concept in that the biopsy specimens, particularly those of distant lymph nodes, presented the microscopic picture of transitional cell carcinoma, while tumor tissue removed from the same sites at autopsy, several weeks or months later, showed typical small cell tumor.

The 3 tumors classified as carcinoma simplex did not fulfil the morphologic criteria of the small cell type, nor could they be satisfactorily classed with the squamous cell carcinomas or adenocarcinomas. The histologic picture was that of large round to polygonal cells loosely arranged in small groups with no differentiation.

GROSS MORBID ANATOMY

Small Cell Carcinoma.—The distribution of the cases according to the location of the tumor in the lung, lobe or bronchus is summarized in table 1. The usual point of origin is at or proximal to the hilus of the lung. In 70 per cent of the cases the tumor involved the main stem bronchus, whereas in 70 per cent of the cases of squamous cell carcinoma the tumor originated in eparterial or hyparterial branches. The bronchus of origin usually shows slight to moderate occlusion by tumor, although diffuse mucosal involvement may occur without apparent ulceration and with no extension into the lumen. In 4 cases the process advanced along the mucosa to the trachea. The growth extends from the bronchus into surrounding tissue and forms an irregular, firm mass which compresses and infiltrates the lung or invades the mediastinum. In 9 of 21 cases of tumor arising in a main stem bronchus, the growth was essentially mediastinal, with only slight parenchymal involvement. The tumor may extend into the lung along smaller bronchi and by way of peribronchial lymphatic vessels. Pleural involvement by tumor was noted in 11 cases, in 8 of which there was bloody effusion. In 18 cases bronchial occlusion resulted in numerous small bronchiectatic abscesses, and in 3 instances there was formation of an abscess cavity, 5 cm. in diameter, lined with a pyogenic membrane and showing no tumor in its wall.

In every case there was conspicuous involvement of the tracheobronchial lymph nodes by tumor, usually with almost complete obliteration of their structure (table 2). A large mass filling the superior or posterosuperior mediastinum was present in 18 of the 35 cases. The aorta and the pulmonary vessels were frequently encased in tumor. There were invasion into and thrombosis of the superior vena cava (5 cases), severe compression and displacement of the esophagus

TABLE 1.—*Distribution of Carcinomas in Lung, Lobe and Bronchus**

	Number of Cases		
	Small Cell Carcinoma	Squamous Cell Carcinoma	Adeno-carcinoma
Lung, 93 cases	34	37	22
Right lung	22	21	11
Left lung	12	16	11
Lobe, 85 cases	30†	36	19
Right lung			
Upper lobe	9	7	4
Middle lobe	1	2	1
Lower lobe	3	6	4
Entire lung	1	6	1
Left lung			
Upper lobe	6	10	7
Lower lobe	1	5	2
Bronchus, 84 cases	30	34	20
Right main	12	6	0
Left main	9	1	2
Eparterial	3	6	2
Hyparterial, middle lobe of right lung	1	2	1
Hyparterial, lower lobe of right lung	2	6	4
Hyparterial, upper lobe of left lung	0	5	6
Hyparterial, lower lobe of left lung	1	5	2
Branch	2	3	3

* Tumors which were described inadequately for the purpose of the table have been omitted.

† Nine of the tumors were essentially mediastinal in position and showed slight or no parenchymal involvement.

TABLE 2.—*Tracheobronchial Lymph Nodes*

	Number of Cases		
	Total	Lymph Node Involvement	Percentage
Small cell carcinoma	33	33	100
Squamous cell carcinoma	36	24	66
Adenocarcinoma	19	16	84

TABLE 3.—*Mediastinal Mass*

	Number of Cases		
	Total	Mediastinal Mass	Percentage
Small cell carcinoma	35	18	52
Squamous cell carcinoma	40	2	5
Adenocarcinoma	22	5	23

TABLE 4.—*Invasion of Heart*

	Number of Cases		
	Total	Invasion of Heart	Percentage
Small cell carcinoma	35	7	20
Squamous cell carcinoma	40	4	10
Adenocarcinoma	22	4	18

(7 cases), with ulceration into the lumen in 4 instances, and lateral or anterior displacement of the trachea (6 cases). Invasion of the pericardium by direct extension occurred at its upper posterior, superior lateral and lateral aspects. Laterally, tumor extended into the pericardium from the mediastinal pleura when these became adherent as a result of infection or tumor infiltration. In 13 cases (37 per cent) there was pericardial involvement, and in 7 of these there was further extension of tumor into the wall of the auricles. In 5 cases in which clinical components of Horner's syndrome were present, tumor was seen at the thoracic inlet, and in 3 of these there was pain in the shoulder and arm due to involvement of the brachial plexus.

Squamous Cell Carcinoma.—Of 37 tumors, 21 were located in the right lung and 16 in the left. The upper lobe was involved with greater frequency than the lower (table 1). The tumor usually begins distal to the bifurcation of the main stem bronchus and not proximal to it, as does the small cell type. Eparterial or hyparterial branches were the site of origin in 24 of 34 cases (70 per cent), and the right main bronchus was involved in 7 cases and branch bronchi in 3 instances. At autopsy there is a firm irregular mass at the hilus. The bronchus of origin shows considerable grayish white, crumbly tumor in its wall, with mucosal ulceration and narrowing of the lumen. The process advances along the mucosa and submucosa toward neighboring large bronchi and the main stem bronchus. Distally there is extension along smaller bronchi into the lung and frequently to the pleura, with serous or bloody effusion. Fatal hemorrhage may result from erosion of large vessels (3 cases). In 5 cases the ribs and the thoracic wall were eroded, an observation confined to the cases of squamous cell tumors. Gradual bronchial occlusion by tumor leads to peripheral bronchiectasis, with the formation of one or several abscess cavities. In 29 of the 40 cases there were small bronchiectatic abscesses (72 per cent), and in 13 cases there was a cavity, 4 cm. or more in diameter, the wall being lined with a pyogenic membrane and infiltrated by tumor. The remaining pulmonary tissue was the seat of atelectasis, chronic interstitial pneumonitis, suppuration and occasionally gangrene. Diffuse bronchiogenic spread of the tumor partly by direct aerogenous transmission led in 8 cases to consolidation of an entire lobe by grayish white soft tumor, with central liquefaction necrosis resulting in cavity formation. Thus the presence of a cavity was noted in 21 of 40 cases of squamous cell carcinoma (table 5).

The squamous cell carcinoma shows no tendency to invade the lymphatic system and metastasize to lymph nodes. However, direct extension from the bronchus of origin into adjacent bronchopulmonary lymph nodes frequently occurs, but even here the infiltration is often

slight and the nodes remain relatively intact and small. Involvement of lymph nodes beyond the hilus of the lung (i. e., tracheobronchial, at the superior or the inferior bifurcation, and paratracheal) occurred in 24 of 36 cases (66 per cent). When the tumor arose from a main stem bronchus, tracheobronchial nodes were invaded in every instance. With origin from eparterial or hyparterial branches in the upper lobe of the left lung, involvement was found in 73 per cent of cases and from hyparterial branches in the lower lobe in 54 per cent. In 2 cases a large tumor formed in the posterosuperior mediastinum (table 3). Tumor involvement of the pericardium usually occurred by direct extension from lymph nodes at the bifurcation, the pericapsular connective

TABLE 5.—*Cavity Formation*

	Number of Cases		
	Total	Cavity Formation	Percentage
Small cell carcinoma	35	3	9
Squamous cell carcinoma	40	21	52
Adenocarcinoma	22	6	27

TABLE 6.—*Squamous Cell Carcinoma with Tracheobronchial Lymph Node Involvement*

	Number of Cases		
	Total	Involvement of Tracheobronchial Nodes	Percentage
Main bronchus	7	7	100
Eparterial and hyparterial branches, upper lobe of left lung	11	8	73
Hyparterial branches, lower lobe	13	7	54
Branch bronchus	3	2	66

tissue of which blends with the fibrous pericardial layer in the superior mediastinum. Thus involvement was at the site of the pericardial reflection over the great vessels at the base of the heart. While such extension was present in 14 cases (32 per cent), invasion of the wall of one or both auricles occurred in only 4 cases (10 per cent).

Adenocarcinoma.—The right and the left lung were involved with equal frequency, and the tumor usually began within the hilus of the lung (table 1). In 20 cases only 2 tumors involved the main stem bronchus, 3 originated in a small branch bronchus and the remaining 15 (75 per cent) involved eparterial or hyparterial branches. The bronchus of origin is occluded by tumor, and the growth extends along the mucosa toward the main stem bronchus and diffusely into the

parenchyma of the lung along small bronchi and bronchioles, the walls being replaced by carcinoma. Pleural infiltration occurred in 11 cases (50 per cent), and in 6 cases there was bloody effusion. Bronchiectatic abscesses were frequent, and in 3 cases there was an abscess cavity, 5 cm. in diameter, showing tumor in its wall. Diffuse spread of the growth by an aerogenous bronchiogenic route led in 3 cases to replacement of an entire lobe by tumor, with central necrosis resulting in cavity formation (table 5). In 16 (84 per cent) of the 19 adequately described cases there was slight to conspicuous involvement of the tracheobronchial lymph nodes by tumor (table 2). Direct extension into the pericardium occurred in 8 instances (36 per cent), with invasion of the myocardium of the right or of the left auricle in 4 cases (18 per cent). Shortly before death 1 patient had auricular flutter, presumably due to involvement of the right auricle by tumor. A large tumor was present in the posterosuperior mediastinum in 5 cases (table 3). In 3 of these cases the aortic arch was partly encased in tumor which involved the recurrent laryngeal and phrenic nerves.

Carcinoma Simplex.—One of the 3 tumors of this type was a circumscribed growth in the lung parenchyma. The other 2 involved hyparterial bronchi and showed extensive invasion of the lung, involvement of tracheobronchial lymph nodes and widespread metastases.

TUMORS OF THE PARENCHYMA AND BRANCH BRONCHI

In 78 of the entire group of 100 cases the tumor involved a main stem, eparterial or hyparterial bronchus. In 10 cases the tumor was not accurately located in relation to the bronchial tree, and in the remaining 12 the major bronchus was free from tumor and the growth either was in the parenchyma of the lung (4 cases) or involved a minor branch bronchus (8 cases).

The parenchymal carcinoma was a circumscribed growth, 5 to 10 cm. in diameter, the origin of which could not be traced to a macroscopically visible bronchus. The mass was situated in the periphery of the lung and extended to the pleura, which in 2 instances showed irregular infiltration. Three of the tumors were squamous cell carcinomas, and 1 was carcinoma simplex. Involvement of the bronchopulmonary lymph nodes was present in 3 cases, and 2 of the tumors showed further extension to tracheobronchial nodes. In only 1 case was there extrathoracic metastasis.

In the 8 cases in which the tumor derived from a branch bronchus there was an irregularly circumscribed growth, which occasionally infiltrated the pleura. In 7 of these cases (2 small cell tumors, 2 squamous cell carcinomas and 3 adenocarcinomas) the tumor was located in the upper lobe. In all cases the regional lymph nodes were involved, and in 5 cases the tracheobronchial nodes were also involved; extrathoracic

metastases occurred in 6 cases. One squamous cell carcinoma situated in a lower lobe showed no lymph node involvement but had metastasized to the adrenal glands.

BIOPSY SPECIMENS REMOVED AT OPERATION

A summary of all the biopsies made during the clinical study of these cases is presented in table 7. These data are of importance in determining the extent and the mode of dissemination of each type of carcinoma. Almost half the specimens of small cell tumor were removed from an extrathoracic site, while the specimens of squamous cell tumor were almost uniformly obtained from within the chest and in the neighborhood of the primary tumor. Among the small cell tumors, extrathoracic superficial lymph nodes represented 45 per cent of the "positive" specimens, while, in striking contrast to this, there were no "positive" lymph node biopsy specimens of the squamous cell type. The majority of the specimens showing adenocarcinoma came from the lung, although several distant sites were represented; lymph nodes, however, were an unimportant source.

Bronchi.—Fifteen (75 per cent) of the 20 specimens obtained bronchoscopically showed carcinoma. The highest percentage of positive results, as might be expected, was obtained in cases of small cell tumor; 70 per cent of these tumors involved the main stem bronchus and would have been readily visualized bronchoscopically. Of the 4 squamous cell carcinomas for which negative results were obtained on biopsy, autopsy showed that 2 originated in hyparterial bronchi of the lower lobe and 2 involved the eparterial branch at its origin without extending into the main stem bronchus.

Pleural Fluid.—A dependable diagnosis of carcinoma based on microscopic examination of the pleural fluid rests on the demonstration of tissue organization of cells with a cytologic structure indicative of tumor. Diagnosis based on the cytologic structure alone or the nuclear-nucleolar ratio [3] is rarely conclusive and is often hazardous. In cases of small cell tumor particularly the loss of tissue organization in a fluid medium may preclude a positive diagnosis, since the individual cells are small and may resemble blood cells and the nuclear structure may be obscured by hyperchromicity. All but one of the effusions showing carcinoma cells in the cases of squamous cell carcinoma and adenocarcinoma were hemorrhagic, and in every instance at autopsy there was tumor infiltration of the pleura. In 1 case of squamous cell carcinoma it was demonstrated that a pleural effusion showing carcinoma

3. Foot, N. C.: Identification of Tumor Cells in Sediments of Serous Effusions, Am. J. Path. **13**:1-12 (Jan.) 1937.

cells may occur before there is any involvement of the tracheobronchial lymph nodes by tumor or any distant metastases.

Lungs.—Autopsy studies were made in 2 cases in which pneumonectomy had been performed for carcinoma. In each instance death occurred four weeks after the operation and was due to the development of a bronchopleural fistula with empyema. Both surgical specimens showed carcinoma involving a hyparterial branch of the lower lobe. In 1 case an adenocarcinoma was revealed at autopsy at the site of excision of the hyparterial bronchus, with involvement of the lymph nodes at the inferior bifurcation and with metastasis to the liver and to

TABLE 7.—*Summary of Biopsy Data*

	Number of Biopsies	Positive Results
Small cell carcinoma, 35 cases (28 biopsies)		
Bronchus	8	7
Cervical node	4	4
Submaxillary node	2	2
Axillary node	3	2
Inguinal node	1	1
Pleural fluid	5	0
Lung tissue	2	2
Skin	3	2
Squamous cell carcinoma, 40 cases (34 biopsies)		
Bronchus	11	7
Intercostal nodes	2	0
Lung, aspiration (4 cases)	6	1
Pleural fluid (4 cases; positive results in 3 cases)	8	5
Lungs	2	2
Lung tissue	2	2
Sputum	1	0
Ilium (1 case)	2	1
Adenocarcinoma, 22 cases (16 biopsies)		
Bronchus	1	1
Right lung	1	1
Cervical nodes	1	1
Lung, aspiration (1 case)	2	0
Pleural fluid (4 cases; positive result in 1 case)	8	2
Skin	2	2
Sputum	1	0

the opposite lung. In the second case a squamous cell carcinoma was shown at autopsy to have been completely resected; there were no metastases.

METASTASES

The postmortem data regarding distribution of metastases are summarized in table 8. These correlate closely with the data regarding distribution of metastases obtained during life. It is again evident that the distinct difference in tendency to metastasis depends on cell type. Only 35 per cent of the squamous cell carcinomas showed extrathoracic dissemination, as compared to 89 per cent of the small cell carcinomas and 86 per cent of the adenocarcinomas.

No close parallel was found to exist between the degree of differentiation of the tumor and the extent of metastasis. The small cell carci-

nomas were undifferentiated and were not subject to grading. The poorly differentiated adenocarcinomas as a general rule showed more widespread metastases than those that were well or partly differentiated. Partly or well differentiated squamous cell carcinomas metastasized less frequently than the poorly differentiated tumors, but the extent of dissemination was approximately the same.

Small Cell Carcinomas.—These are vigorously metastasizing tumors with a tendency to diffuse permeation of the lymphatic system. Groups of lymph nodes were involved by this type of tumor as follows: tracheobronchial, 100 per cent of cases; cervical, 48 per cent; abdominal, 48 per cent; axillary, 8.5 per cent, and inguinal, 5.7 per cent. The presence of carcinoma in superficial lymph nodes of the cervical, axillary

TABLE 8.—*Metastases*

	Small Cell Carcinoma, Percentage	Squamous Cell Carcinoma, Percentage	Adeno-carcinoma, Percentage	Total, Percentage
Cervical nodes	48.0	0	27.0	22
Axillary nodes	8.5	0	0	3
Submaxillary nodes	8.5	0	0	3
Inguinal nodes	5.7	2.5	4.5	3
Abdominal nodes	48.0	12.0	27.0	27
Liver	66.0	18.0	50.0	40
Adrenal glands	54.0	12.0	64.0	38
Kidneys	20.0	15.0	36.0	21
Other lung	11.0	12.0	55.0	21
Bone	23.0	10.0	32.0	19
Pancreas	40.0	0	18.0	18
Skin	14.0	2.5	23.0	11
Spleen	17.0	0	23.0	11
Heart	5.7	2.5	23.0	7
Thyroid gland	8.5	0	4.5	4

Miscellaneous (number of cases):
Small cell carcinoma: gallbladder 2, pituitary body 1, bladder 1, uterus 1, cecum 1, ileum 1, colon 1, peritoneum 1
Adenocarcinoma: gallbladder 2, colon 2, mesentery 2, omentum 3, stomach 1, peritoneum 1, diaphragm 4

or inguinal chains was uniformly indicative of extensive involvement of deeper groups in the thorax and abdomen. Of the organs and systems, the liver, adrenal glands and pancreas were most frequently the site of metastasis (66, 54 and 40 per cent, respectively), with the brain, skeletal system, kidneys and spleen following in that order. The skin was involved in 14 per cent of the cases. As a rule the liver was extensively replaced by tumor, the average weight of this organ in 23 cases being 2,950 Gm. The heaviest livers weighed 6,275, 6,200 and 5,200 Gm., respectively. In these cases the patient showed signs and symptoms of portal obstruction—ascites, jaundice and melena. The adrenal glands usually showed small circumscribed tumor nodules in the medulla and occasionally were almost completely obliterated by larger confluent masses. Involvement of the pancreas was more than twice as frequent in these cases as in the cases of adenocarcinoma. Solitary or

multiple nodules were present in the head, body or tail of the organ, and in 4 cases there was complete replacement of the tip of the tail by tumor.

Squamous Cell Carcinomas.—The squamous cell carcinomas are infiltrating, relatively nonmetastasizing tumors. In 65 per cent of the cases autopsy revealed no extrathoracic metastases; this is consistent with the fact that practically all the biopsy specimens that showed this type of tumor were obtained from the lung itself. Extensive dissemination by way of the lymphatic system does not occur, and involvement other than that of the regional lymph nodes is infrequent. The cervical and axillary chains were not involved at all, and the abdominal nodes showed invasion in 12 per cent, with 1 instance of extension to the inguinal nodes. The liver, adrenal glands and kidneys were involved in only 18, 12 and 15 per cent of the cases, respectively. There were no instances of metastases to the spleen or to the pancreas, and the heart and skin were involved only once. Metastatic tumor of the opposite lung was found in 5 cases (12 per cent). In only 6 of the 21 cases of cavity formation was there extrathoracic dissemination. Moreover, erosion of the thoracic wall and ribs by tumor occurred in 4 cases in which no metastatic lesions were observed.

Adenocarcinomas.—These tumors metastasize essentially by way of the blood stream, in contrast to small cell carcinomas, which are disseminated chiefly by way of the lymphatic system. Organs, systems and regions usually invaded by a hematogenous route, such as the kidneys, adrenal glands, skeletal system, opposite lungs, skin and heart, were more frequently involved by adenocarcinoma than by the small cell tumor. Metastasis to the opposite lung occurred in 55 per cent of cases, and the skin and heart were each involved in 23 per cent of cases. As is the case with the small cell type of tumor, the cutaneous metastases are usually found in the anterior thoracic wall and the abdomen, the lesions consisting of small, round, freely movable subcutaneous nodules, occasionally attached to the corium. There was no instance of ulceration through the skin. The heart usually showed isolated circumscribed tumor nodules, 2 mm. to 1 cm. in diameter, situated subendocardially in the ventricular myocardium or the interventricular septum. Cardiac arrhythmia was not detected during the clinical study in these cases. The adrenal glands were the organs most frequently involved by this type of tumor (64 per cent), often extensively, with almost complete destruction. Invasion of the liver and pancreas by this type of tumor was both less frequent and less extensive than for the small cell carcinoma. The average weight of the 10 livers showing metastases was 1,780 Gm. Involvement of lymph nodes was more frequent than in the cases of squamous cell carcinoma but much less extensive and con-

spicuous than in the case of small cell carcinoma. Abdominal and cervical nodes were each invaded in 27 per cent of the cases. Extension to the inguinal nodes occurred only once, and there was no instance of involvement of the axillary or submaxillary lymph nodes.

METASTASES TO THE BRAIN

Metastatic tumor of the brain was found in 22 per cent of the entire group of cases. However, the frequency of involvement again

TABLE 9.—*Metastases to the Brain*

	Number of Cases	Number of Examinations	Number of Cases of Metastasis	Percentage
Small cell carcinoma	35	12	4	33.0
Squamous cell carcinoma	40	19	1	5.3
Adenocarcinoma	22	14	5	36.0
All types	97	45	10	22.0

TABLE 10.—*Clinical Data*

	Small Cell Carcinoma	Squamous Cell Carcinoma	Adeno-carcinoma
Total number of cases	35	40	22
Age distribution:			
30-39	5	1	3
40-49	13	11	6
50-59	13	12	7
60-69	3	11	5
70-79	1	5	0
80-89	..	..	1
Average age	46 years	56 years	51 years
Sex:			
Men	33	38	16
Women	2	2	6
Race:			
White	33	36	18
Negro	2	4	4
Duration of symptoms	6 months	12 months	8 months

showed a distinct difference according to the cell type (table 9). In the cases of small cell carcinoma and adenocarcinoma there were metastases in 33 and 36 per cent of the cases, respectively. These consisted of multiple round, circumscribed nodules, 0.5 to 3 cm. in diameter, in the hemispheres, basal ganglions, midbrain and cerebellum. Clinically the lesions produced weakness or paralysis of the extremities, aphasia and headaches and were mistaken for cerebrovascular accident, cerebral thrombosis or encephalomalacia. Only 1 of the 19 brains examined in cases of squamous cell carcinoma showed metastasis, a solitary tumor, 6 cm. in diameter, in the temporo-occipital lobe. In this case a clinical diagnosis of primary tumor of the brain had been made.

CLINICAL OBSERVATIONS

The distribution of the tumors according to the age, sex and race of the patients is shown in table 10. The patients with small cell carcinoma showed an average age incidence of 46 years; thus this type of tumor affects younger persons than the squamous cell carcinoma or the adenocarcinoma. The ratio of men to women in the entire series was 9 to 1, but for patients with adenocarcinoma it was only 2.7 to 1. The ratio of white to Negro patients in the 100 cases of carcinoma was 9 to 1, as compared with a ratio of 3 to 1 for all white and Negro patients who came to autopsy in the period studied.

Symptoms.—Cough with or without expectoration, thoracic pain, hemoptysis and dyspnea were the most frequent symptoms in each of the three groups of cases. The complaints in the cases of squamous cell carcinoma were almost uniformly referable to the respiratory system. The chief complaints in 4 cases of adenocarcinoma were due to metastatic lesions, i. e., slow speech, vomiting, pathologic fracture of the cervical portion of the spine and pain in the back. In the cases of small cell carcinoma the frequent formation of a mediastinal tumor was responsible for a triad of symptoms—dyspnea of the obstructive type, dysphagia and dysphonia—not observed in the other cases. Dysphonia is an infrequent symptom in cases of adenocarcinoma and is rare in cases of squamous cell carcinoma. Abdominal pain and vomiting referable to metastases were occasionally prominent in the cases of small cell carcinoma. Two patients with small cell carcinoma entered the hospital complaining of a mass in the neck. The total duration of symptoms from onset to death averaged six months in the cases of small cell carcinoma, twelve months in the cases of squamous cell carcinoma and eight months in the cases of adenocarcinoma. In each of the groups medical aid was usually sought late in the course of the disease.

Tumor of the Superior Pulmonary Sulcus.—No case fulfilling all the criteria for this tumor, as originally defined by Pancoast,[4] was found in the present study. However, in 5 cases of small cell carcinoma and in 1 case of squamous cell carcinoma there were components of the "group complex" of the tumor, such as pain in the shoulder and arm, atrophy of the muscles of the hand, pupillary changes and a roentgenogram showing a shadow at the extreme apex (with local costal involvement in 1 case). In every instance these were associated with tumor at the thoracic inlet.

Clinical Diagnosis.—The correct clinical diagnosis was made in 56 of the 100 cases of carcinoma. Over the entire period of eleven years

4. Pancoast, H. K.: Superior Pulmonary Sulcus Tumor: Tumor Characterized by Pain, Horner's Syndrome, Destruction of Bone, and Atrophy of Hand Muscles, J. A. M. A. **99**:1391-1396 (Oct. 22) 1932.

the incidence of correct diagnoses was approximately the same for each of the three groups. In the last five years of the study, i. e., 1933 to 1937, inclusive, there was no essential increase in the number of cases of squamous cell carcinoma or adenocarcinoma in which a correct diagnosis was made. However, in 14 (80 per cent) of the 17 cases of small cell carcinoma for this period the correct diagnosis was made, as compared to 4 (22 per cent) of the 18 cases for the preceding six years. In the cases of squamous cell carcinoma the chief source of error was the masking of the tumor by suppurative inflammation, with a resulting picture of pulmonary abscess (6 cases). Carcinoma was mistaken for tuberculosis in 4 cases. In the cases of adenocarcinoma the incorrect final impressions were: carcinoma of unknown origin with metastases (4 cases); pulmonary tuberculosis (2 cases), and carcinoma of the esophagus, encephalomalacia and pleural effusion (1 case each). In 9 cases of small cell tumor a tentative diagnosis of a malignant growth with metastases was made, but the site of origin was incorrectly ascribed: i. e., the stomach (4 cases); thyroid gland, prostate and kidney (1 case each), and mediastinum (sarcoma; 2 cases). Pulmonary tuberculosis and pulmonary abscess were each diagnosed in 3 cases of small cell carcinoma.

Preceding Pulmonary Disease.—Frequently the clinical history did not give sufficient information to warrant conclusive interpretation. However, all but a few patients stated that they were in good health prior to the onset of the present illness. A past history indicating chronic pulmonary infection, such as bronchitis or bronchiectasis, was conspicuously absent. Five patients gave a history of chronic cough of one to four years' duration. Only 2 had influenza (during the epidemic of 1917), and in none of the records was there a history of previous tuberculosis. At autopsy active tuberculosis was present grossly in only 2 per cent and healed tuberculosis in 5 per cent of the cases. Pneumonoconiosis was anatomically diagnosed in 5 cases. These percentages are in accord with the postmortem incidence of tuberculosis and pneumonoconiosis in a control group of unselected cases. In the 2 cases of active tuberculosis the lesions were acute and minimal in extent and probably developed during the course of the carcinoma rather than before it.

Pulmonary Suppuration.—That primary carcinoma of the lung is frequently masked by secondary pulmonary suppuration is a well known fact. This was found to be especially true of squamous cell carcinoma which is an invasive, infiltrating tumor accompanied by infection, necrosis and the formation of an abscess cavity. Not infrequently, combined clinical and roentgenographic studies do not conclusively differentiate between tumor and abscess of the lung, or they demonstrate only the

latter when both are present. Yet the diagnosis is of great importance, since surgical therapy may be indicated, especially for this type of tumor, which showed metastases in 29 per cent of cases, as compared to 42 per cent for the cases of noncavitating carcinoma. Bronchoscopy is invaluable in establishing a diagnosis and should be carried out in all cases of pulmonary suppuration when the patient is over 40 years of age. Autopsy showed that this procedure would have demonstrated tumor in the 9 cases in which an erroneous diagnosis of pulmonary abscess was made.

Tumors of the Parenchyma and Branch Bronchi.—Of 12 patients with tumor showing no relation to the major bronchus, 4 had no pulmonary symptoms. In 2 of these cases the tumor was incidentally observed at autopsy; in 2 others the only complaints were referable to metastatic tumor of the spine, and the primary site of the carcinoma was not discovered. The pulmonary symptoms of the remaining 8 patients, for 6 of whom a correct diagnosis was made, were few in number, consisting chiefly of cough and thoracic pain. The duration of the disease from clinical onset to death was approximately the same in this group of cases as for the cases of tumor involving the major bronchus.

COMMENT

The histologic classification of primary bronchiogenic carcinoma can be correlated with essential differences in the growth and dissemination, clinical course and prognosis in cases of each type of tumor.

The small cell carcinoma is a highly malignant tumor which metastasizes extensively and shows a tendency to widespread extension through the lymphatic system. The growth usually occurs at the hilus of the lung and infiltrates the surrounding parenchyma or grows into the posterosuperior mediastinum. Dissemination also occurs to a lesser extent by a hematogenous route. The tumor affects younger persons, and there is a rapid clinical course without notable remission. The prognosis is poor. At the onset or in the early stage of growth the tumor is surgically inaccessible. There is at present no convincing evidence of the efficacy of roentgen therapy.[5]

The squamous cell carcinoma offers the most favorable prognosis for surgical resection. The tumor is locally invasive and infiltrating and shows little tendency to metastasize. Invasion of lymph nodes occurs slowly and is usually of slight degree. In the early stage of growth the tumor may be entirely within the hilus of the lung, and complete removal can be accomplished by pneumonectomy. Autopsy studies indi-

5. Graham, E. A., and Singer, J. J.: Successful Removal of the Entire Lung for Carcinoma of the Bronchus, J. A. M. A. **101**:1371-1374 (Oct. 28) 1933. Edwards, A. T.: Surgical Treatment of Intrathoracic New Growths, Brit. M. J. **1**:827-830 (May 7) 1932. Graham, E. A.: Primary Carcinoma of the Lung or Bronchus, Ann. Surg. **103**:1-12 (Jan.) 1936.

cate that with earlier clinical recognition an appreciable number of patients with this type of carcinoma could be treated surgically. One case in which complete resection was achieved, in spite of a clinical history of ten months' duration, is included in this study. The slow growth of this type of tumor, which is reflected in the comparatively long clinical course, is a distinctly favorable factor as regards prognosis. The tumor involving a hyparterial bronchus in the lower lobe appears to offer the best prognosis for complete resection, since it invades the tracheobronchial lymph nodes less frequently than do tumors in other locations (table 6).

The opportunity afforded for surgical treatment is less favorable in the case of adenocarcinoma than in the case of squamous cell carcinoma. Though the former tumor is locally invasive and infiltrating, it shows more frequent and extensive involvement of lymph nodes and metastasizes vigorously and by preference by way of the blood stream. Since the tumor occurs within the hilus of the lung, early clinical recognition renders surgical intervention feasible prior to involvement of the tracheobronchial lymph nodes or extrathoracic metastasis. Moreover, for this type of tumor, pneumonectomy may be warranted later in the course of the disease in the hope of alleviating symptoms and possibly prolonging life.

CONCLUSIONS

The histologic classification of primary carcinoma of the lung may be correlated with essential differences in the growth, dissemination and prognosis typical of each type of tumor.

The small cell carcinoma is a highly malignant tumor which offers a poor prognosis. Usually primary at the hilus of the lung, it readily invades the posterosuperior mediastinum and metastasizes extensively, with especial tendency to widespread extension through the lymphatic system. The tumor occurs in younger persons, and there is a short, rapid course without notable remission.

The squamous cell carcinoma is a slowly growing, locally invasive and relatively nonmetastasizing tumor accompanied by infection, necrosis and cavity formation. Involvement of lymph nodes other than the regional and tracheobronchial nodes is infrequent. This type of carcinoma, particularly a growth involving the hyparterial bronchus of the lower lobe, offers the most favorable prognosis for complete resection.

In cases of adenocarcinoma, surgical intervention is less favorable, since the tumor, while locally invasive, shows more frequent and more extensive lymph node involvement and metastasizes vigorously by way of the blood stream.

Dr. Howard T. Karsner and Dr. Herbert S. Reichle advised concerning this study.

Progress in Internal Medicine

GASTROENTEROLOGY

A REVIEW OF THE LITERATURE FROM JANUARY 1937 TO JUNE 1938

CHESTER M. JONES, M.D.

THOMAS V. URMY, M.D.

EDWARD B. BENEDICT, M.D.

MILTON H. CLIFFORD, M.D.

AND

BENJAMIN V. WHITE, M.D.

BOSTON

A review of the literature on the gastrointestinal tract covering 1937 and the first half of 1938 must present at best a composite picture. Owing to the complicated mechanism by which the digestive tract is controlled, it is obvious that searchers after more or less isolated facts must frequently be at variance. The known variables involving the processes of digestion are becoming increasingly more numerous. Because of this fact it is more and more difficult to draw definite and lasting conclusions as to etiologic or physiologic processes.

From the anatomico-pathologic point of view little new has been added during the period covered, although there has been a constantly increasing number of observations on some of the rarer conditions. Observations based on clinical studies or animal experimentation obviously represent attempts to elucidate certain fundamentals, and discrepancies between individual investigations still serve to show how delicate and how involved is the motor and secretory function that has to do with the ingestion, preparation, absorption and elimination of food products. It is of interest that more and more scrutiny is being directed toward the relation between the central nervous system, the autonomic nervous system and the digestive tract. The importance of the psyche in its influence on digestive processes is being more clearly and logically presented. Applied pharmacology in relation to gastrointestinal physiology is increasingly productive of results, which are still, however, confused and at times discordant. Therapeutic methods are being

From the Department of Medicine of the Massachusetts General Hospital and the Department of Medicine of the Harvard Medical School.

revised on the basis of physiologic studies and clinical results but, as usual, leave much to be desired.

The present review attempts to discuss in a more or less logical sequence what have seemed to be the most important and outstanding clinical and experimental studies.

THE ESOPHAGUS

Dilatation of the esophagus has been considered from several angles. Strauss,[1] in careful studies on autopsy specimens in 5 cases, noted that dilatation started above the area where the esophagus goes through the diaphragm. In younger subjects he believes that such dilatation may be due to constriction by the crura of the diaphragm, whereas in older persons he believes that most frequently it is due to relaxation of the esophageal hiatus.

Etzel [2] presents evidence that lesions of Auerbach's plexus are not necessarily the result or the cause of esophageal dilatation. His observations were made at autopsy in 2 carefully studied cases and on sections of the esophagus of a dog with experimental constriction of that organ.

McGibbon and Mather [3] present data on a small group of cases in which there were areas of spasm of the esophagus at a level well above the cardia. The spasm at times gave the appearance of a so-called functional diverticulum and was transient or intermittent in some and persistent in others. It appeared to be a neurologic manifestation, at times associated with disease of other organs.

An interesting study on so-called cardiospasm is that of Lendrum,[4] based on a complete autopsy study of 150 controls, numerous animals and 13 patients with "cardiospasm." No evidence was found histologically of a true sphincter at the cardia, although there were more adventitial elastic fibers at the level of the cardia than in the middle portion of the esophagus. The myenteric plexus appeared to be the same throughout the lower two thirds of the esophagus. Histologic studies in 13 cases of "cardiospasm" showed, among other anatomic changes, a marked decrease in the number of ganglions of Auerbach's plexus in comparison with the number in control material previously studied.

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1. Strauss, H.: Ueber hiatogene oder phrenogene Oesophagusdilatation, Arch. f. Verdauungskr. **61**:158, 1937.

2. Etzel, E.: La dilatación del esófago frente a las lesiones del plexo de Auerbach en el megaesófago, Bol. y trab. de la Soc. de cir. de Buenos Aires **21**: 131, 1937.

3. McGibbon, J. E. G., and Mather, J. H.: Simple Non-Sphincteric Spasm of the Esophagus, Lancet **1**:1385, 1937.

4. Lendrum, F. C.: Anatomic Features of the Cardiac Orifice of the Stomach, with Special Reference to Cardiospasm, Arch. Int. Med. **59**:474 (March) 1937.

Jönsson [5] gives an interesting roentgenographic study of the hypopharynx and the upper portion of the esophagus in 50 normal persons, at least 18 of them showing definite bulging in the posterior wall and immediately below the cricoid cartilage, corresponding to the so-called esophageal lip of Killian. Such a finding is at times incorrectly interpreted as a sign of a foreign body. Jönsson presents in detail the anatomic relations at the esophageal mouth and discusses the correspondence between the so-called esophageal lip and a pulsion diverticulum.

Of moderate interest is the report of Wallace,[6] who reviewed the histories of 26 patients for whom a roentgen diagnosis of traction diverticulum of the esophagus had been made. Contrary to the usual conception that such diverticula are most frequently asymptomatic, over one third of Wallace's patients presented symptoms, varying from acute hematemesis to substernal pain and dysphagia.

Benedict and Daland [7] present the curious complication of benign stricture of the esophagus and duodenal ulcer, with a discussion of previously reported cases.

Of slight interest is the report by Piquet and Tison [8] on the apparent relation between alcoholic addiction and cancer of the esophagus. Of 110 patients with cancer of the esophagus, 102 were exceedingly heavy drinkers.

The surgical treatment of cancer of the esophagus still presents almost insuperable technical difficulties. Several successful operations on individual patients have been noted, however, and Garlock [9] reports in detail on 3 patients who were successfully operated on for lesions of the thoracic portion of the esophagus. The technic and the preoperative and postoperative care are described in great detail.

THE STOMACH

Numerous studies have been carried out regarding the relation between the central nervous system and the control of gastric secretion. Heslop,[10] in a carefully performed set of experiments on cats and dogs,

5. Jönsson, G.: Notes on the X-Ray Picture of the So-Called Esophagus Lip, Acta radiol. **18**:452, 1937.

6. Wallace, R. P.: Traction Diverticulum of the Esophagus, Arch. Int. Med. **60**:454 (Sept.) 1937.

7. Benedict, E. B., and Daland, E. M.: Benign Stricture of the Esophagus Complicating Duodenal Ulcer, New England J. Med. **218**:599, 1938.

8. Piquet, J., and Tison: Alcool et cancer de l'oesophage, Bronchoscop., œsophagoscop. et gastroscop., April 1937, p. 137.

9. Garlock, J. H.: Operation Cancer of the Esophagus, Surg. Gynec. & Obst. **66**:535, 1938.

10. Heslop, T. S.: The Nervous Control of Gastric Secretion: An Experimental Study, Brit. J. Surg. **25**:884, 1938.

for the most part confirmed previous experimental work on this subject. He concludes from his observations that the response of gastric secretion to histamine is independent of nervous influences. Pure acid juice was obtained after stimulation with histamine, despite section of the fibers of the splanchnic and vagus nerves. He thinks that the secretion of mucus by the stomach is partly under the control of the sympathetic portion of the autonomic nervous system and that the splanchnic nerves contain parasympathetic as well as sympathetic fibers. Localized stimulation of the anterior and posterior portions of the hypothalamus produced parasympathetic and sympathetic effects.

Various investigators have elaborated on Cushing's earlier suggestions on the relation between a lesion of the midbrain and concurrent ulceration of the stomach or duodenum. Koga [11] reports experiments on rabbits with injury to the region of the third ventricle. In one third of the experimental animals there were hemorrhages and erosions in the gastric mucous membrane, while there were none in the control animals. Fifty per cent of 18 animals after resection of the vagus nerve below the diaphragm showed similar lesions, while 60 per cent of 32 animals after resection of the splanchnic nerve and the solar and superior mesenteric ganglions showed gastric lesions. It was thought that the lesions were due to local secretory disturbances and that they were different from the usual peptic ulcer.

The experimental lesions of the central nervous system produced by Chiariello [12] were fundamentally in accord with those just noted. Lesions involving the optic thalamus in dogs, along with other nuclei to some extent, were associated with hemorrhagic changes in the gastric mucosa. The author believes that these vascular lesions are fundamental and that they are characteristic of severe lesions of the midbrain but have nothing in common with true peptic ulcer. They show, he thinks, only that certain points of the nervous system, especially of the optic thalamus, are true trophic centers for the mucosa of the digestive tube.

Martin and Schnedorf,[13] in a study on monkeys and cats, produced small isolated lesions by electrocoagulation in the hypothalamic area. Unlike the findings in the previous studies, in which the trauma to the brain tissue was undoubtedly much more extensive, all the autopsy observations, as well as studies of the stools and vomitus, failed to

11. Koga, H.: Tierexperimentelle Untersuchung über die Magenveränderung bei der Läsion des Vorderhirns und des autonomen Nervensystems, Arch. f. klin. Chir. **188**:449, 1937.

12. Chiariello, A. G.: Lesioni sperimentali del sistema nervoso centrale ed ulcera gastrica, Rassegna internaz. di clin. e terap. **18**:489, 1937.

13. Martin, J., and Schnedorf, J. G.: The Absence of Changes in Gastric Activity and of Gastro-Intestinal Ulceration Following Hypothalamic Lesions in the Monkey and Cat, Am. J. Physiol. **122**:81, 1938.

show any evidence of gastric ulceration. There were also no changes in gastric secretion.

The case presented by Vanzant [14] of a duodenal ulcer with melena, apparently occurring twenty days after an acute injury of the brain, is of interest in relation to Cushing's cases and to the aforementioned experimental work.

Vascular gastric lesions, similar to those just referred to, were procured by Dodds [15] in rabbits after the subcutaneous injection of an extract of the posterior lobe of the pituitary body. If the gastric contents were neutralized by the administration of alkali previous to the administration of the extract, no lesions were produced. Extract of the anterior lobe appeared to have no effect. Extract of the posterior lobe, however, when given by mouth, apparently had a direct local effect in producing ulceration. Dodds believes that his findings confirm the idea that the secretion of the posterior lobe of the pituitary body is essential to normal gastric secretion but that at present it is impossible to apply these experiments clinically.

By inference, Snapper's [16] report on 5 patients with insufficiency of the anterior lobe of the pituitary body and associated complete gastric achylia is of interest, suggesting as it does a possible physiologic effect of the anterior lobe on gastric secretion.

That gastric secretion is only in part mediated by the vagus nerves is verified by the observations of Nicolini,[17] who performed numerous gastric analyses on a group of patients with postencephalitic Parkinson's disease who were receiving atropine therapy. In spite of evidences of paralysis of the vagus nerve after use of the drug, it was not possible consistently to reduce the gastric acidity. As in previous investigations, varying effects of the drug on gastric secretion were noted, but the writer stresses particularly that gastric secretion apparently can be entirely independent of vagal activity.

Gastric secretory studies after standardized surgical procedures, while inconclusive, are still of some interest. Holman and Sandusky [18] completely review the literature on gastric acidity after gastroenterostomy and point out the wide variation in the results which have been reported.

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14. Vanzant, F. R., and Brown, J. A.: A Case of Peptic Ulcer in a Child Following Brain Injury, Am. J. Digest. Dis. & Nutrition **5**:113, 1938.

15. Dodds, E. C.: Recherches récentes sur le lobe postérieur de l'hypophyse, Paris méd. **2**:274, 1937.

16. Snapper, I.: Relation Between Anterior Pituitary Insufficiency and Function of Stomach and Bone Marrow, Nederl. tijdschr. v. geneesk. **81**:265, 1937.

17. Nicolini, E.: La funzione secretoria dello stomaco in rapporto alla somministrazione cronica di forti dosi di belladonna (ricerche su encefalitici in cura bulgara), Studium **28**:97, 1938.

18. Holman, C., and Sandusky, W. R.: Gastric Acidity After Gastro-Enterostomy, Am. J. M. Sc. **195**:220, 1938.

They call attention to the pitfalls of secretory studies after the Ewald test meal. By using a more careful technic, consisting of the constant suction method of Bloomfield and Polland and stimulation with histamine, they found that the actual acidity of the gastric secretion was not materially altered by posterior gastroenterostomy in 92 per cent of 75 patients investigated. This appeared to be true in practically all cases, regardless of the duration of time after operation. The authors conclude that the titratable acidity determined before and after operation cannot be used as a prognostic criterion of the therapeutic results of gastroenterostomy.

Strauss and Necheles and their associates,[19] after detailed studies made on 44 patients who had been subjected to subtotal gastrectomy for ulcer, conclude that there is no real correlation between clinical results and certain physiologic variables, such as the emptying time of the stomach, the hunger motility of the stomach, the gastroscopic appearance of the stomach, gastric analysis, preoperative anemia and clinical symptoms. The only constant finding, according to these investigators, is the correlation between the postoperative results and the gain in or loss of weight. Somewhat similar conclusions were arrived at by Gorvett and Talbot.[20] In 26 carefully studied cases these investigators were unable to find any correlation between the preoperative gastric acidity and the postoperative level, although in 65 per cent of the cases the Ewald meal showed postoperative achlorhydria. No constant changes in the blood were noted postoperatively. The emptying time of the stomach after operation in four fifths of the cases was less than three and one-half hours (at the lower limit of normal), but one fifth of the patients still had a normal emptying time. There was no evidence of gastric dilatation in any of the cases. Eighty per cent of the patients maintained their weight or gained weight after operation. The patients were studied at periods of from five months to two years after operation.

Two rather interesting observations on gastric secretion are presented by Schiff [21] and by Brown and Dolkart.[22] Schiff carried out nearly 80 separate gastric analyses for a single patient over a period of four and one-half years. Gastric secretion was stimulated by the use of histamine. There was a definite variation in the level of gastric

19. Strauss, A. A.; Strauss, S.; Levitsky, P.; Scheman, L.; Lerdmon, E. E.: Arens, R. A.; Meyer, J., and Necheles, H.: Physiological and Clinical Study of Patients After Subtotal Gastrectomy, Am. J. Digest. Dis. & Nutrition **4**:32, 1937.

20. Gorvett, E. A., and Talbot, E. S.: Physiologic and Symptomatic Expectancy Following Subtotal Gastrectomy, Am. J. M. Sc. **193**:345, 1937.

21. Schiff, L.: Gastric Secretion in Man: Observations on the Effects of Repeated Injections of Histamine and on Transient Achlorhydria, Arch. Int. Med. **61**:774 (May) 1938.

22. Brown, C. F. G., and Dolkart, R. E.: Gastric Acid During Recurrences and Remissions of Duodenal Ulcer, Arch. Int. Med. **60**:680 (Oct.) 1937.

acidity over this period, and it is interesting to note that temporary periods of relative achlorhydria were observed. There was no evidence that repeated stimulation with histamine caused fatigue of the secretory apparatus; and with the dosage used, there was no evidence of abnormal gastric symptoms. It is also interesting to note that the intrinsic antianemic factor was present in all the samples obtained, including those taken during periods of achlorhydria. Brown and Dolkart made observations on 20 patients and 5 controls, the average period of observation being a little over three years. An average of 50 gastric analyses were made for each patient with the Ewald meal. Fifteen of the patients had duodenal ulcers, which had been present for an average of eleven years. Careful observations regarding seasonal incidence and recurrences of the ulcer seemed to indicate that although gastric acidity varied widely, there was no relation between the level of acidity and the degree of symptoms present or any other evidence of ulcer activity. A second group of patients with ulcer failed to show any significant reduction of acidity during fasting while under strict treatment of the Sippy type or otherwise. These studies are chiefly important because of the long period of observation and because of the demonstration of wide fluctuations of gastric secretion in normal and diseased patients.

Another set of clinical observations on gastric secretion is that of Comfort, Butsch and Eusterman,[23] who examined the gastric secretory activity of 79 patients in whom cancer of the stomach developed after the first gastric analysis. The average length of time intervening between the first gastric analysis and the subsequent diagnosis of cancer of the stomach was six years. Twenty-eight of the patients retained free acid at a practically unchanged level even after the development of cancer. Achlorhydria developed during the six years in those patients particularly who originally had low values for acid. Although these studies are of some interest, they give little further information as to the histologic relation between achlorhydria and cancer of the stomach. They suggest, however, that a diminution in the secretory activity of the stomach per se has no causative relation to the development of cancer.

An added item of some interest is the finding of Fabian [24] that the amount of salivary secretion is reduced in gastric cancer, achylia gastrica and pernicious anemia but particularly in pernicious anemia. This diminution is essentially one of quantity, as the chloride content of the saliva is only slightly diminished and the ferment content not at all.

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23. Comfort, M. W.; Butsch, W. L., and Eusterman, G. B.: Observations on Gastric Acidity Before and After the Development of Carcinoma of Stomach, Am. J. Digest. Dis. & Nutrition **4**:673, 1937.

24. Fabian, G.: Untersuchungen über die Speichelsekretion bei Magencarcinom, perniziöser Anämie und Achylia gastrica, Ztschr. f. klin. Med. **131**:403, 1937.

Studies of gastric motility continue to indicate the existence of various factors influencing this function. Andersen [25] demonstrated by means of an intragastric balloon attached to a kymograph that the administration of food through a duodenal tube was associated with absolute lack of gastric constriction provided the stomach was emptied. The presence of a little food in the stomach appeared to initiate gastric motor activity, which was already slightly modified by duodenal feeding. The results of these experiments are mainly confirmatory of the already known value of duodenal feedings in intragastric disease.

The effect of bilateral resection of the splanchnic nerves on gastric motility was studied by Barron and Curtis [26] in 2 cases. Observations on the gastric motor mechanism were made before operation. Subsequent to unilateral resection of the splanchnic nerves there was no change in the average rate of gastric emptying, but after bilateral resection there was a decrease of well over an hour in the emptying time, with a definite increase in the number and in the amplitude of the contractions and a marked increase in the duration of periods of gastric motility. These findings were noted for at least seven months.

Sleeth and Van Liere [27] demonstrated in dogs that a low environmental temperature decreased the emptying time of the stomach, whereas an elevation of the temperature surrounding the body increased it. At 15 F. the gastric emptying time was 17 per cent less than normal, and at 90 F. it was increased 10 per cent. The same investigators [28] also found that the administration of digitalis definitely decreased the emptying time of the stomach in healthy young men. The administration of 5 cc. of tincture of digitalis mixed with a standard test meal reduced the gastric emptying time from 13 to 25 per cent. Clinical confirmation of these studies is apparently afforded by Hollander's [29] observations on 5 patients with so-called pylorospasm. After the administration of two thirds of a digitalizing dose by Eggleston's method, the administration of tincture of digitalis produced definite relief in all 5 patients when added to a regime that had previously been unsuccessful in controlling their symptoms.

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25. Andersen, M.: Gastrographic Studies Under Administration of Food Through Duodenal Tube, Acta med. Scandinav. **93**:437, 1937.

26. Barron, L. E., and Curtis, G. M.: Late Effects of Bilateral Resection of Splanchnic Nerves on Human Gastric Motor Mechanisms, Am. J. Physiol. **120**: 356, 1937.

27. Sleeth, C. K., and Van Liere, E. J.: Effect of Environmental Temperature on Emptying Time of Stomach, Am. J. Physiol. **118**:272, 1937.

28. Van Liere, E. J., and Sleeth, C. K.: Immediate Effect of Tincture of Digitalis on the Emptying Time of the Human Stomach, Arch. Int. Med. **61**: 83 (Jan.) 1938.

29. Hollander, E.: Treatment of Pylorospasm with Digitalis: Report of Five Cases, Am. J. Digest. Dis. & Nutrition **4**:158, 1937.

Studies on the hunger mechanism were carried out by Manville and Munroe,[30] who performed ileogastrostomy on dogs and observed motor and secretory activity after the administration of 10, 20 or 25 per cent solution of dextrose intragastrically. They found, as have previous observers, that hunger contractions were inhibited by the introduction of dextrose solution into the stomach. The reappearance of gastric motility was not always associated with a drop in the blood sugar content. Dextrose solution so introduced was also found to inhibit gastric motor activity induced with pilocarpine hydrochloride and insulin, and a similar inhibitory effect was obtained on gastric secretion provoked with histamine, pilocarpine hydrochloride, insulin and sham feedings. The investigators feel that there was genuine dissociation between secretory and motor activity.

Lalich, Youmans and Meek [31] studied in dogs the effect of insulin on gastric motility. The injection of insulin into intact dogs has previously shown an augmentation of gastric motility, but after vagotomy the stimulation is replaced by inhibition, even though the gastric musculature may recover some of its tonus. This inhibitory effect of insulin on gastric motility after vagotomy persisted after section of the splanchnic nerves, after removal of the celiac ganglions and after removal of one adrenal gland and the medullary portion of the other. The authors believe that they have obtained evidence that the normal stimulating effect of insulin on gastric motility is through the vagal centers and that the inhibition of gastric motility becomes apparent only with elimination of abdominal vagal stimulation.

An interesting set of experiments on the factor of muscle spasm in the etiology of jejunal ulcer was carried out by Fauley and Ivy.[32] These were similar to previous experiments performed on dogs by Steinberg and Starr. The latter investigators concluded from their experiments that muscle spasm is essential to the formation of jejunal ulcer. The procedure consisted in performing gastrojejunostomy and at the same time denudation of the muscular layers of the jejunum adjacent to the anastomosis after the duodenal contents had been diverted into the terminal portion of the ileum. In the original experiments, ulcer did not develop in the denuded area. The experiments conducted by Fauley and Ivy were identical except that the anastomosis was end to end instead of side to side. Of 14 dogs successfully operated on, 13 died of ulcer at the usual site in from ten to twenty-three weeks.

30. Manville, I. A., and Munroe, W. R.: Studies on the Gastric Hunger Mechanism: II. The Inhibitory Effect of Dextrose Solutions, Am. J. Digest. Dis. & Nutrition **4**:561, 1937.

31. Lalich, J.; Youmans, W. B., and Meek, W. J.: Insulin and Gastric Motility, Am. J. Physiol. **120**:554, 1937.

32. Fauley, G. B., and Ivy, A. C.: The Factor of Spasm in the Etiology of Jejunal Ulcer, Am. J. Digest. Dis. & Nutrition **4**:160, 1937.

and the findings led to the conclusion that local muscular spasm is not essential to the development of jejunal ulcer after gastrojejunostomy.

The effect of various drugs on gastric secretion has been a source of study for several years. In a carefully prepared paper Babkin [33] discusses in detail the physiologic action of histamine. There is extensive reference to the literature but no detailed description of his own unpublished experimental work. He aims to show that in the normal processes of gastric secretion during which histamine is liberated or as a result of the subcutaneous administration of histamine, of electric stimulation of the vagus nerves or of sham feedings in dogs with esophagotomy, there is an inherent possibility of pathologic disturbances which may eventually lead to damage of the gastric or duodenal wall so as to result in peptic ulcer. The suggestions contained in this work are stimulating although not new. The article presents a fairly comprehensive résumé of this conception of gastric secretory activity. The author says that Necheles' theory of ulcer formation due to the output of acetylcholine is "tempting" but finds inconsistencies in it.

Rivers and Vanzant,[34] using a double histamine test, i. e., a second injection of histamine one hour after the original administration of the drug, found nearly an equal increase in the amount of gastric pepsin after each injection of histamine. They conclude that histamine not only washed out the preformed pepsin but also stimulated increased production of the ferment.

Necheles,[35] following the knowledge that parasympathetic stimulation liberates acetylcholine and that stimulation of the gastric division of the vagus nerve causes acetylcholine to appear in the venous blood from the stomach, attempted a new approach to the genesis of peptic ulcer. Perfusion experiments in rats and dogs show that acetylcholine tends to produce anoxemia of the gastric tissues, which theoretically would be more marked over those areas most richly supplied with vagus fibers. He postulates the hypothesis that ulcer may frequently be due to an overproduction of acetylcholine in such areas in patients who are subject to excessive autonomic stimulation.

Experiments by Necheles, Motel, Kosse and Neuwelt [36] on the action of acetylbetamethylcholine and prostigmin on gastric secretion in

33. Babkin, B. P.: The Abnormal Functioning of the Gastric Secretory Mechanism as a Possible Factor in the Pathogenesis of Peptic Ulcer, Canad. M. A. J. **38**:421, 1938.

34. Rivers, A. B., and Vanzant, F. R.: A Study of Peptic Activity by Means of the Double Histamine Test, Am. J. Digest. Dis. & Nutrition **4**:304, 1937.

35. Necheles, H.: A Theory on the Formation of Peptic Ulcer, Am. J. Digest. Dis. & Nutrition **4**:643, 1937.

36. Necheles, H.; Motel, W. G.; Kosse, J., and Neuwelt, F.: The Effect of Acetyl-Beta-Methyl-Choline and Prostigmine on the Secretion of the Stomach of Man and Dog, Am. J. Digest. Dis. & Nutrition **5**:224, 1938.

man and dog attempted to further the aforementioned hypothesis. These workers showed in dogs with a Heidenhain pouch an increase in gastric acidity, in volume of gastric secretion and in pepsin secretion after injections of acetylbetamethylcholine. They found that this drug and histamine were synergistic in relation to gastric secretion. The drug stimulated gastric secretion in human beings, provided care was taken to avoid the swallowing of saliva. Saliva was found to inhibit the secretion of gastric acid induced by the drug. Somewhat similar results were obtained with prostigmin, and the authors take care to advise against the use of either of these two drugs in the treatment of peptic ulcer, as proposed in the literature. The experiments of Banting [37] on overstimulation of the parasympathetic nervous system by acetylbetamethylcholine in animals seems to confirm Necheles' view. Banting found lesions typical of peptic ulcer in the stomach of his animals, in addition to a certain number of colonic lesions.

The effect of aluminum preparations on gastric acidity and secretory activity was studied by Ivy and his associates.[38] They found in 6 graduate students who were accustomed to using the stomach tube that the administration of aluminum preparations reduced free acidity for forty-five minutes or longer. There was a variation in individual subjects, and a definite tendency to an increase in acidity after aluminum had been evacuated was characteristic of 4 of the subjects.

Beazell, Schmidt and Ivy [39] also carried out observations on the effect of aluminum hydroxide on absorption from the gastrointestinal tract. By in vitro experiments it was shown that the activity of pancreatin was unaltered by the presence of aluminum hydroxide. In 3 dogs, liberal amounts of aluminum hydroxide cream, when added to a day's ration, increased the total bulk of the stools but produced no increase in the nitrogen or fat content.

Culmer, Atkinson and Ivy [40] demonstrated that solution of hydrogen peroxide acts as a definite depressant of gastric acidity. There appears to be wide individual variation. Apparently the stronger the solution of hydrogen peroxide, the greater the depression of gastric acidity. The authors believe, however, that the drug is not a satisfactory clinical

37. Banting, F. G., and Hall, G. E.: The Experimental Production of Myocardial and Coronary Artery Lesions, Tr. A. Am. Physicians **52**:204, 1937.

38. Ivy, A. C.; Terry, L.; Fauley, G. B., and Bradley, W. B.: Effect of Administration of Aluminum Preparations on Secretory Activity in Gastric Acidity of Normal Stomach, Am. J. Digest. Dis. & Nutrition **3**:879, 1937.

39. Beazell, J. M.; Schmidt, C. R., and Ivy, A. C.: The Effect of Aluminum Hydroxide Cream on Absorption from the Gastrointestinal Tract, Am. J. Digest. Dis. & Nutrition **5**:164, 1938.

40. Culmer, C. U.; Atkinson, A. J., and Ivy, A. C.: Hydrogen Peroxide as a Depressant of Gastric Acidity, Am. J. Digest. Dis. & Nutrition **4**:219, 1937.

preparation and point out that its use in the treatment of ulcer is associated with the danger of precipitating an acute hemorrhage. These findings are of interest in view of the use of solution of hydrogen peroxide in the treatment of gastritis, wherein only beneficial results have been claimed for it.

Studies on the cephalic (psychic) phase of gastric secretion have been carried on by Wilhelmj, McCarthy and Hill.[41] In a brief study it has been shown that the presence of tenth-normal hydrochloric acid in the stomach and in the upper portion of the intestine causes definite inhibition of the intragastric chemical and intestinal phases of acid secretion. In most instances these authors are able to show that the psychic phase of acid secretion can break through the inhibitory effect produced by the presence of acid in the stomach and duodenum and can cause a fairly high rate of acid secretion. The secretory energy of the psychic phase of gastric secretion may often exceed that due to the intragastric or intestinal phases, and it is believed that it is possible for the psychic phase of secretion to be responsible for a degree of hyperacidity unattainable by the other two phases alone.

Some scattered observations related to gastric physiology are of interest:

The bactericidal power of gastric juice, which has long been recognized, has been studied by Sebastianelli.[42] Studies carried out on a large number of specimens of gastric juice appeared to show that the bactericidal power of whole gastric juice on colon bacilli is much greater than that due to gastric acidity alone. Gastric juice which is intensely acid possesses little, if any, greater bactericidal power than gastric juice of low acidity.

Thiele[43] records that values for the calcium content of the blood run parallel with the titratable gastric acidity. The calcium content is especially low in cases of gastric carcinoma, and the intravenous administration of calcium appears to increase the gastric acidity.

Christiansen[44] has continued to make observations on azotemia, which is often associated with fever in gastrointestinal hemorrhage. This may be present in the absence of vomiting or associated renal disease. The striking increase in the urea content of the blood after massive intraintestinal hemorrhage is discussed, and various possible

41. Wilhelmj, C. M.; McCarthy, H. H., and Hill, F. C.: Acid Inhibition and Cephalic (Psychic) Phase of Gastric Secretion, Am. J. Physiol. **120**:619, 1937.

42. Sebastianelli, A.: Sul potere battericida del succo gastrico: Rapporti fra acidità e potere battericida del succo gastrico, Policlinico (sez. prat.) **44**:1593, 1937.

43. Thiele, W.: Magenacidität und Kalkstoffwechsel, Klin. Wchnschr. **16**: 165, 1937.

44. Christiansen, T.: Biochemical Changes in the Organism Produced by Massive Intraintestinal Hemorrhage, Rev. Gastroenterol. **4**:166, 1937.

explanations are offered for its occurrence. None of these explanations seems adequate either to the author or to the reviewers, but the chemical finding is of interest.

Another isolated finding involving the chemical analysis of the blood is that of Offenkrantz and Feraro,[45] who studied the cholesterol content of the serum of patients with peptic ulcer. The total cholesterol value was significantly lower than normal figures. This reduction appeared to be due to a fall in the value for cholesterol esters. The authors attempt no explanation but feel that the finding is of some interest and significance in view of the fact that most of the patients were being treated with the high fat diet common to most ulcer regimens.

Although of little practical value, the study of the diastase content of the blood of patients with ulcer by Probstein, Gray and Wheeler [46] is of some clinical interest. Diastase determinations were obtained for 9 patients who came to autopsy as a result of an acute perforated ulcer. In the 3 cases in which the ulcer involved the pancreas, the diastase content was found to be moderately elevated above normal. In 1 instance it was at an exceedingly high level and was well within the range of values found in acute pancreatitis. In the 5 cases in which the pancreas was not involved, the values obtained were all normal. The authors conclude that a normal or low diastase value not only rules out acute pancreatitis, as is generally accepted, but also rules out penetration of a peptic ulcer into the pancreas.

Hollander [47] suggests a modification of the Bloomfield-Keifer technic of gastric analysis. He observes that the use of phenolphthalein as a dilution indicator in gastric analysis is unsatisfactory because of loss by precipitation at a high p_H; he suggests the substitution of phenolsulfonphthalein (phenol red).

Woldman [48] suggests a new simple test for the determination of a break in the continuity of the mucous membrane of the gastrointestinal tract. The test is based on the fact that phenolphthalein given by mouth is excreted almost in toto in the feces. Unless large amounts are taken, that appearing in the urine is in the conjugated form and does not give an immediate color reaction with sodium hydroxide. The test consists of the introduction of 1 per cent alcoholic solution

45. Offenkrantz, F. M., and Feraro, F.: A Study of Serum Cholesterol in Patients with Peptic Ulcer, J. Lab. & Clin. Med. **22**:780, 1937.

46. Probstein, J. G.; Gray, S. H., and Wheeler, P. A.: Blood Diastase in Acutely Perforating Peptic Ulcer, Proc. Soc. Exper. Biol. & Med. **37**:613, 1938.

47. Hollander, F.; Penner, A., and Saltzman, M.: Determination of Phenol Red in Gastric Contents, Proc. Soc. Exper. Biol. & Med. **36**:568, 1937.

48. Woldman, E. E.: A Simple Test for Determining the Presence of Gastrointestinal Lesions, Am. J. Digest. Dis. & Nutrition **5**:221, 1938.

of phenolphthalein by mouth during fasting and the testing of the urine at two and four hour intervals. If phenolphthalein appears in the urine, this is interpreted as evidence that there is a break in the gastrointestinal mucous membrane. For 212 patients and normal persons the test is said to have been correct, with an error of less than 3 per cent.

Crohn and Shwartzman [49] present an interesting and probably important paper on recurrences of ulcer in association with infection of the upper respiratory tract. The clinical fact appears to be well established and is familiar to most clinicians. The authors propose that the Shwartzman phenomenon is operative in such recurrences and believe that a state of reactivity is set up in patients with ulcer by secondary bactericidal invaders. Once this state is set up, local infection may be produced by viruses or by bacteria which produce infection in the intestinal organs. Several examples of recurrences of ulcer, especially with hemorrhage, are presented in association with intercurrent infection of the respiratory tract.

The experimental production of peptic ulcer continues to interest numerous investigators. In an earlier portion of this review, allusion was made to various theories of ulcer formation, either by abnormal stimulation of the autonomic nervous system or by the local action of acetylbetamethylcholine, histamine or other substances. Of the various methods for the experimental production of ulcer that have been recently reported, the following are chosen, not as providing absolutely new material but as exemplifying stimulating investigative work.

Stalker, Bollman and Mann [50] carried out numerous observations on experimental ulcers due to cinchophen. They previously described this method in the production of peptic ulcer in dogs, after the original findings of Churchill and Van Wagoner. In the present studies the authors confirmed the results of their previous investigations; in 77 dogs given cinchophen they found an incidence of 96 per cent of ulcer formation. The larger the dose, the more rapid the formation of the ulcer. For the most part, the ulcer was found on the lesser curvature of the stomach, although a few duodenal ulcers were noted. The use of bone in the diet seemed to extend ulcer formation but did not delay

49. Crohn, B. B., and Shwartzman, G.: Ulcer Recurrences Attributed to Upper Respiratory Tract Infection, Am. J. Digest. Dis. & Nutrition **4**:705, 1938.

50. Stalker, L. K.; Bollman, J. L., and Mann, F. C.: Prophylactic Treatment of Peptic Ulcers Produced Experimentally by Cinchophen, Am. J. Digest. Dis. & Nutrition **3**:822, 1937; Effect of Cinchophen on Gastric Secretion: Experimental Study, Arch. Surg. **34**:1172 (June) 1937; Experimental Peptic Ulcer Produced by Cinchophen, ibid. **35**:290 (Aug.) 1937. Bollman, J. L.; Stalker, L. K., and Mann, F. C.: Experimental Peptic Ulcer Produced by Cinchophen, Arch. Int. Med. **61**:119 (Jan.) 1938.

healing after the use of cinchophen. Regardless of the method of administration, cinchophen produced ulcers. A characteristic of the cinchophen ulcer is that it starts with destruction of the mucosa and progresses as does peptic ulcer in man. From observations made on animals on which various agents were employed that are used in the treatment of ulcer in human beings, the authors conclude that gastric acidity is an important factor in the production of a cinchophen ulcer. The taking of alkaline powders or milk or gastroenterostomy preceding the administration of cinchophen prevented the formation of an ulcer. Other measures were less efficacious. Exclusion of the pylorus prior to the administration of cinchophen prevented the formation of an ulcer in the excluded portions. Studies of gastric secretion led to the conclusion that the administration of cinchophen resulted in no change in the level of acidity. There appeared to be hypersecretion when the ulcer had fully developed, followed by hyposecretion with omission of the drug. The ulcer produced was usually single and was found on the lesser curvature of the stomach. It appeared to be preceded by acute gastritis, which was less severe after the first two weeks. An ulcer of the perforating type developed in three weeks and gave the appearance of being chronic.

Simonds,[51] in a histologic study of the material originally described by Van Wagoner and Churchill, summarizes his conclusions as follows: "The feeding of old cinchophen to dogs is the most effective method of producing peptic ulcers, resembling in all essentials the spontaneous ulcer in man." Histologically the sequence of events is that of severe gastritis, which may be diffuse and mild and is accompanied by plasma cell infiltration of the mucosa; or it may be focal and may be characterized by the formation of small abscesses in any level of the mucosa. This gastritis occurs apparently within twenty-four hours after the initial feeding of cinchophen and therefore precedes the ulcer. It is believed to be an important factor in its causation.

The principle of the production of ulcer by the exclusion of bile from the small bowel is not new. Various methods have been tested, but the study of DeBakey [52] on the relative productive value of these is noteworthy in that it reveals the conflicting interests in the experimental production of ulcer in dogs and also attempts to place the relative value of three components of the duodenal juices in the prevention of ulcer formation. The author has attempted to obtain comparable data in his experiments by using a similar technic for all dogs with only

51. Simonds, J. P.: Mode of Origin of Experimental Gastric Ulcer Induced by Cinchophen, Arch. Path. **26**:44 (July) 1938.

52. DeBakey, M. E.: Peptic Ulceration: The Relative Protective Value of the Alkaline Duodenal Juices, Arch. Surg. **34**:230 (Feb.) 1937.

minor variations. In each instance the pylorus was severed, and the gastric and duodenal ends were closed. In addition, four variations were introduced: anterior gastroenterostomy, transplantation of the main pancreatic duct of the terminal portion of the ileum, transplantation of the common bile duct of the terminal portion of the ileum and transplantation of both the pancreatic and the common bile duct. In these procedures the production of ulcer was, respectively, 50, 70, 90 and 100 per cent. The author's results, although drawn from relatively few animals, agree with the majority of conclusions stated in the literature —of the constituents of alkali in the duodenal juices, bile has the most significance in preventing the formation of jejunal ulcer; succus entericus is of the least importance, and pancreatic secretion lies between the two.

Hanke,[53] by the creation of an external biliary fistula after section of the common bile duct, produced a duodenal ulcer in each of 7 dogs. Factors that were considered in the production of the ulcer were absence of the normal neutralizing action of the bile and a possible diminution of mucosal resistance to the metabolic and hepatic disturbances resulting from the diversion of the bile. Hanke draws the inference that of the many factors involved in the production of a peptic ulcer in man, changes in the biliary secretion may represent an important one.

Volini, Widenhorn and Finlayson[54] confirmed the previous production of jejunal ulcer in dogs by means of the Exalto and Mann-Williamson methods of diverting the duodenal contents from the stomach and jejunum. The particular finding of interest in their experiments, however, is not elsewhere reported in the voluminous literature on these methods of producing experimental ulcer. These authors noted not only typical acute, subacute or chronic ulcer in the jejunum; but, in addition, in more than half their experimental animals a similar ulcer was found in the excluded duodenum. No satisfactory explanation is suggested, although they feel that trauma can be excluded.

The effect of physiologic hypersecretion with the production of long periods of concentration of hydrochloric acid and pepsin in the gastric juice was studied by Schmidt and Fogelson.[55] A similar work was carried out by Silbermann in 1927. The present experiments, however, failed to produce ulcer by sham feedings in esophagotomized dogs,

53. Hanke, H.: Gastroduodenale Ulcerationen nach totaler Ableitung der Galle, Arch. f. klin. Chir. **187**:675, 1937.

54. Volini, I. F.; Widenhorn, H. O., and Finlayson, U.: Experimental Duodenal Ulcer, Surg., Gynec. & Obst. **65**:159, 1937.

55. Schmidt, C. R., and Fogelson, S. J.: The Effect of Physiologic Hypersecretion on the Gastroduodenal Mucosa, Am. J. Physiol. **120**:87, 1937.

although the animals were studied over much longer periods than in the original experiments and were carried on maintenance and deficient diets, with at times the addition of extra hydrochloric acid introduced through a gastrostomy opening. The conclusion is that acid gastric juice per se is not sufficiently destructive to overcome other factors which inhibit or prevent gastroduodenal ulceration.

Considerable interest has been attached to the relation between ulcer and dietary deficiency. For the most part these studies have been concerned particularly with vitamin C. Numerous reports in the literature have confirmed observations that low blood values for vitamin C are the rule for patients with peptic ulcer, particularly when there has been any tendency to pyloric obstruction with associated malnutrition and prolonged rigid dietary treatment or hemorrhage. Hanke [56] claims to have noted the frequent occurrence of mucosal ulcer in the pyloric region of the stomach and in the upper portion of the duodenum in guinea pigs kept on a diet deficient in vitamin C. In animals given a diet adequate in vitamin C, such lesions do not occur.

Ingalls and Warren [57] were among the first to indicate the deficiency of ascorbic acid in the blood plasma of patients with ulcer and to emphasize the probable wisdom of vitamin C therapy. A previous paper by Lanman and Ingalls [58] brings out the relation between vitamin C deficiency and wound healing. In this study the writers were apparently convinced that in animals receiving a diet deficient in vitamin C abdominal wounds tended to heal less rapidly and less firmly than those in animals receiving a normal diet. Under conditions of ascorbic acid deficiency the wounds tended to rupture spontaneously. Whether vitamin C deficiency has any etiologic relation to the ulcer problem is still a moot point. As noted previously, there is little doubt that low vitamin C values are of frequent occurrence in cases of ulcer, but that such a deficiency has anything to do with the causation of ulcer is still to be determined.

Elder and Emery,[59] after a careful analysis of the eating habits of 25 patients with ulcer and 25 controls, came to the conclusion that peptic ulcer is not a deficiency disease, in the usual sense of the term.

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56. Hanke, H.: Experimentelle Erzeugung und Pathogenese von C-Vitaminmangelgeschwüren des Magens, Klin. Wchnschr. **16**:1205, 1937.

57. Ingalls, T. H., and Warren, H. A.: Asymptomatic Scurvy: Its Relation to Wound Healing and Its Incidence in Patients with Peptic Ulcer, New England J. Med. **217**:443, 1937.

58. Lanman, T. H., and Ingalls, T. H.: Vitamin C Deficiency and Wound Healing: An Experimental and Clinical Study, Ann. Surg. **105**:616, 1937.

59. Elder, M., and Emery, E. S., Jr.: Food Habits of Patients with Peptic Ulcer, Am. J. Digest. Dis. & Nutrition **4**:493, 1937.

A comparison of the dietary histories obtained from these two groups with a theoretically normal diet led them to believe that there is no significant difference, with the exception that the intake of vitamin C is possibly a little low in patients with ulcer. They believe that if peptic ulcer is a deficiency disease the deficiency is an intrinsic factor and is not associated with a deficient intake of food. There is suggestive evidence that vitamin C deficiency may be related to one of the complications of ulcer—hemorrhage. Portnoy and Wilkinson [60] studied 107 subjects by various methods and showed to their satisfaction that patients with peptic ulcer, especially those with hematemesis, have marked vitamin C deficiency.

In contrast to the analysis made by Elder and Emery, the study made by Bourne [61] on 87 subjects, 42 of whom had ulcer, showed that hospital patients receiving diet for ulcer exhibited a significantly greater degree of capillary fragility than did normal persons or patients with other diseases. However the author is unwilling to conclude that lack of vitamin C is of etiologic significance. Rivers and Carlson [62] also agree with previous authors that most patients receiving an approved diet for ulcer have an insufficient intake of ascorbic acid. They feel that this is particularly true of patients with repeated hemorrhages, and they speculate as to the possibility that the hemorrhagic factor may be influenced by vitamin C deficiency.

The underlying question of vitamin C deficiency is still not clearly understood, but it is highly probable that the findings represent the results of a deficiency secondary to the original ulcer condition rather than a causative relation to the formation of the ulcer. It is probable that the intelligent administration of vitamin C to patients with ulcer who show a lack of ascorbic acid is a rational therapeutic procedure. There is some reason for believing that it may correct a hemorrhagic tendency and may aid in ulcer healing, although this is far from proved. There is also a suggestion that it may lead to more normal convalescence after a gastrointestinal operation when deficiency exists. In this connection the studies of Reedman [63] on the ascorbic acid content of milk are of some interest. From his work it follows that milk alone will not supply sufficient vitamin C in the diet, although it is

60. Portnoy, B., and Wilkinson, J. F.: Intradermal Test for Vitamin C Deficiency, Brit. M. J. **1**:328, 1938.

61. Bourne, G.: Vitamin C Deficiency in Peptic Ulceration Estimated by the Capillary Resistance Test, Brit. M. J. **1**:560, 1938.

62. Rivers, A. B., and Carlson, L. A.: Vitamin C as a Supplement in the Therapy of Peptic Ulcer, Proc. Staff Meet., Mayo Clin. **12**:383, 1937.

63. Reedman, E. J.: Ascorbic Acid Content of Milk, Canad. Pub. Health J. **28**: 339, 1937.

equally true that it is not normally required to do so. A pint (473 cc.) of pasteurized milk may be said to contain 10 mg. of cevitamic acid.

Hoelzel and Da Costa [64] carried out extensive observations on rats and mice receiving a diet deficient in protein or in the essential amino acids. Ulceration of the prestomach and main stomach of rats and the duodenum of mice was frequent and was regarded as objective evidence of "protein hunger or amino-acid hunger." Cheney [65] similarly produced gastric ulcer in chicks by giving a diet devoid of alfalfa and grain. Studies of gastric secretion were carried out on these as well as on control animals, and it was found that chicks with gastric ulcer had hyperacidity. The increased acidity in chicks with ulcer over those without ulcer suggested to the author that it is a result and not a direct cause of the lesion.

Another interesting effect of hypoproteinemia on plasmapheresis is presented in the study of Barden, Ravdin and Frazier.[66] After a Billroth I or II operation dogs were subjected to repeated plasmapheresis and a low protein diet. It was noted that there was marked retardation of the gastric emptying time after the production of hypoproteinemia, and the investigators mention work in progress which also suggests a definite slowing of motility of the small intestine under the same conditions. They explain the reduction in emptying time as possibly being due to nutritional edema of the operative stoma, a hypothesis previously suggested by Jones and Eaton.

PEPTIC ULCER

In a clinical discussion of ulcer an interesting report is presented by Hansen,[67] who has collected the records of about 14,000 patients with gastric and duodenal ulcer treated medically in certain Danish hospitals since 1900. In the first decade of the century the incidence of ulcer in women was much greater than that in men. In the second decade the numbers were approximately equal for the two sexes, and in the third and fourth decades there was a striking increase in the incidence of ulcer in men, at present about three fourths of all patients being men. The author is unable to explain this remarkable change in relative frequency of the disease.

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64. Hoelzel, F., and Da Costa, E.: Production of Peptic Ulcers in Rats and Mice by Diets Deficient in Protein, Am. J. Digest. Dis. & Nutrition **4**:325, 1937.

65. Cheney, G.: Gastric Acidity in Chicks with Experimental Ulcer, Am. J. Digest. Dis. & Nutrition **5**:104, 1938.

66. Barden, R. P.; Ravdin, I. S., and Frazier, W. D.: Hypoproteinemia as a Factor in the Retardation of Gastric Emptying After Operations of the Billroth I or II Types, Am. J. Roentgenol. **38**:196, 1937.

67. Hansen, J. L.: Investigations on the Frequency of Peptic Ulcer with Special Regard to Distribution Between the Two Sexes: Fourteen Thousand Cases, Ugesk. f. læger **99**:1145, 1937.

An article by Tomoda [68] is of interest as indicating the incidence of gastric ulceration in Japan. Four and seven-tenths of over 8,000 autopsies showed gastric ulcer, whereas duodenal ulcer was found in only 0.5 per cent of 6,000 necropsies. In Japan, apparently, gastric and duodenal ulcers occur with much greater frequency in men, while in Europe and America gastric ulcer appears with greater frequency in women.

Comparative data from China, as presented by Chang,[69] show that the incidence of peptic ulcer in 2,000 consecutive autopsies was 1.7 per cent, a much lower rate than that noted in Japan. The ratio between males and females suffering from this condition was 3.3 to 1.

In 1931 the Division of Vital Statistics in Washington reported a mortality rate for ulcer of the stomach of 4.2 per cent, with the rate for ulcer of the duodenum being only 1.9 per cent, a combined mortality rate of 6.1 per cent. Portis and Jaffé [70] present the incidence of peptic ulcer in 9,171 consecutive necropsies performed at the Cook County Hospital, Chicago, between 1929 and 1936. There were 457 cases of peptic ulcer, or a total incidence of about 5 per cent. The incidence of peptic ulcer in white subjects was 5.23 per cent and in Negroes 3.5 per cent.

All the aforementioned articles are interesting from the point of view of distribution and occurrence of peptic ulcer. The last article referred to contains many interesting statistical facts regarding the location of ulcer, the relation of ulcer to death and other points of interest. One of the best recent summaries of the problem is that presented by Crohn.[71] It contains nothing new as far as clinical or investigative data are concerned but gives an excellent discussion of the entire problem; it is conservative, convincing and well worth the trouble of reading. Blackford, Smith and Affleck [72] also present an interesting study based on 916 patients with ulcer seen in private practice. Attention is particularly directed toward a consideration of the problem of hemorrhage and perforation.

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68. Tomoda, M.: Chirurgische Erfahrungen über Magen- Duodenalgeschwüre auf Grund von 433 Fällen in Japan, Arch. f. klin. Chir. **190**:134, 1937.

69. Chang, C. C.: Acute Perforated Peptic Ulcer: Analysis of Thirty-Seven Operated Cases, Chinese M. J. **52**:161, 1937.

70. Portis, S. A., and Jaffé, R. H.: A Study of Peptic Ulcer Based on Necropsy Records, J. A. M. A. **110**:6 (Jan. 1) 1938.

71. Crohn, B. B.: Gastroduodenal Ulcer: Etiology, Treatment and End Results, New England J. Med. **218**:148, 1938.

72. Blackford, J. M.; Smith, A. L., and Affleck, D. H.: Peptic Ulcer Emergencies: A Study of Massive Hemorrhage and Acute Perforations Treated During the Diagnosis of Nine Hundred and Sixteen Private Cases Suffering from Peptic Ulcers, Am. J. Digest. Dis. & Nutrition **4**:646, 1937.

A rather interesting study of peptic ulcer in pregnancy is presented by Parturier-Lanegrace.[73] The paper is a fairly detailed discussion of only 2 patients, but the implications appear to be that pregnancy may have a temporarily favorable effect on the course of peptic ulcer. This is in line with subsequent observations on the use of estrogen as a therapeutic measure.

The absence of peptic ulcer in patients suffering from pernicious anemia does not prove that acid alone is the important etiologic factor in the production of ulcer, but Kahn's[74] review of 840 cases of pernicious anemia is of interest. For none of this large group of patients with typical Addison's anemia was a diagnosis of chronic peptic ulcer made during the time that the patient was in the hospital. One is inclined to agree with Kahn that at least normal acidity is one of the conditions necessary for the development of chronic peptic ulcer.

The occurrence of ulcer in association with syphilis of the central nervous system has long been noted. The report of Parsons and his associates[75] is of some interest in this connection. Two hundred patients with syphilis of the central nervous system were compared with a group of 400 other patients in the same hospital. The second group, which included patients with latent syphilis, pulmonary tuberculosis and other diseases not involving the central nervous system, showed an incidence of ulcer which was much higher than that for the first group. Patients with neurosyphilis showed an incidence of ulcer of 10.5 per cent, a figure which is much higher than that reported from other clinics in this country, whereas the control groups showed one of less than 3 per cent. No adequate explanation for the high incidence of ulcer in neurosyphilitic patients is given, and the authors feel that syphilis does not appear to be of true etiologic significance in such cases.

A rare observation was made by Hartung and Warkany[76] in a case of meningococcic meningitis. The patient was a boy of 6 years who was admitted to the hospital with typical meningitis and who improved under specific therapy. On the twelfth day after the onset of the disease a fatal hemorrhage occurred from an ulcer of the duodenum, which on section showed, among other organisms, groups of

73. Parturier-Lanegrace, M.: Ulcères et grossesses, Arch. d. mal. de l'app. digestif. **26**:1092, 1936.

74. Kahn, J. R.: Absence of Peptic Ulcer in Pernicious Anemia, Am. J. M. Sc. **194**:463, 1937.

75. Parsons, E. H.; Plummer, D. E.; Ewalt, J. R., and Gaskill, R. C.: Peptic Ulcer in Syphilis of the Central Nervous System, J. A. M. A. **110**:1991 (June 11) 1938.

76. Hartung, C. A., and Warkany, J.: Duodenal Ulcer as a Cause of Death in a Case of Meningococcic Meningitis, J. A. M. A. **110**:1101 (April 2) 1938.

biscuit-shaped gram-negative diplococci, having a structure similar to that of the organisms in the meninges. It is suggested that the ulcer was a result of the meningococcic infection and was analogous to the infection observed in children with ulcer by Gerdine and Hemholtz.

Bloch and Serby [77] add to the accumulated literature on juvenile ulcer, reporting 5 old cases, 8 new cases and 4 additional cases in which the ulcer started early in life. Although the clinical observations are not new, the authors contributed to a better understanding of a rather infrequent diagnosis. They stress the frequency of a family history of ulcer in many of these cases.

An interesting diagnostic comment is found in the report of Paine and Rigler,[78] who made observations on 13 patients incidental to the production of diagnostic pneumoperitoneum. They demonstrated on these patients, as well as on 5 cadavers, that at times as small a quantity of gas as 5 cc. could be demonstrated roentgenographically in the right subphrenic space. In 17 per cent of 38 cases of perforation of the stomach or duodenum, free gas was observed.

Several articles have been written on the subject of atypical localization of pain in relation to gastroduodenal ulcer. Savignac [79] reports 14 cases of gastroduodenal ulcer in which the pain was entirely outside the epigastrium. The pain was periodic and was relieved by alkalis and food. Pain was noted in the thorax, in the axillary region and in the precordial region and was similar to angina or the girdle type of pain found in intercostal neuralgia. In 3 cases the pain was located in the dorsolumbar region and in 3 others in the right upper quadrant of the abdomen. In 3 instances the pain was lower in the abdomen. A more general discussion of the analysis of pain in gastroduodenal ulcer is found in an article by Savy and his associates.[80] The article is analogous to the preceding one and in an excellent discussion brings out the unusual variations in the pain. Mixter [81] calls particular attention to the pain in the back in cases of lesions of the gastrointestinal tract and reports 7 cases of ulcer of the posterior wall

77. Bloch, L., and Serby, A. M.: Peptic Ulcer in Children: A Follow-Up Study of Cases Reported Previously and a Report of Additional Cases, Am. J. Digest. Dis. & Nutrition **4**:15, 1937.

78. Paine, J. R., and Rigler, L. G.: Pneumoperitoneum in Perforations of Gastrointestinal Tract, Surgery **3**:325, 1938.

79. Savignac, R.: La localisation extra-épigastrique de la douleur de l'ulcère gastro-duodénal, Arch. d. mal. de l'app. digestif **27**:751, 1937.

80. Savy, P.; Froment, R.; Chapuy, A., and Jeune, M.: Les anomalies de la douleur dans l'ulcère gastro-duodénal, Presse méd. **45**:609, 1937.

81. Mixter, W. J.: Back Pain in Lesions of the Gastrointestinal Tract with Particular Reference to Duodenal Ulcer, Am. J. Digest Dis. & Nutrition **4**:736, 1938.

in which pain in the back was the sole or predominating symptom. These cases are of particular interest since the patient is usually first seen by the orthopedic surgeon or the neurologist and not infrequently the diagnosis of ulcer is postponed until some complication makes it apparent. These anomalies of pain in cases of ulcer are described clinically and experimentally by Jones,[82] and a correlation is drawn between the experimental production of pain and exact clinical observations.

Among other forms of ulcer therapy, treatment with histidine has received considerable attention. The original experimental results of Weiss and Aron on dogs after the Mann-Williamson operation were apparently definite, and exploitation by pharmaceutic houses rapidly followed. Insufficient substantiation of therapeutic hopes, however, has led to more critical investigation. Fürth and and Scholl [83] state that they were able to corroborate the work of Weiss and his associates, namely, that the cure of an artificially produced ulcer can be accelerated with tryptophan. After much experimentation a method was developed by which injections of histamine produced gastric ulcer in guinea pigs. Whereas ulcer developed in the animals that were treated only with histamine, the simultaneous administration of tryptophan prevented the development. Histidine proved less effective than tryptophan. Practically all other evidence fails to support the idea that histidine is of practical or experimental value. A curious report is that of Jacob and Israel [84] who show that the ampules of 4 per cent solution of histidine which were utilized for the treatment of gastric ulcer between the years 1933 and 1935 contained approximately 0.1 mg. of histamine. Considering that the histamine content might be the effective therapeutic agent, these authors treated a series of patients with daily injections of 0.1 mg. of histamine, with complete clinical success. Such results, however, appear to be an excellent example of wishful thinking and do little to clarify the subject.

By far the most conclusive attack on the subject of histidine therapy is that of Sandweiss,[85] who presents an excellent set of observations. His contribution has a twofold purpose: first, to present clinical data evaluating the results of parenteral therapy in peptic

82. Jones, C. M.: Digestive Tract Pain, New York, The Macmillan Company, 1938.

83. Fürth, O., and Scholl, R.: Ueber den Einfluss des Tryptophans und Histidins auf durch Histamin hervorgerufene Magengeschwüre, Wien. klin. Wchnschr. **50**:1353, 1937.

84. Jacob, A., and Israel, L.: Le traitement de la crise douloureuse de l'ulcère gastro-duodénal par l'histamine à petites doses, Presse méd. **46**:210, 1938.

85. Sandweiss, D. J.: Comparative Results with Dietetic, Parenteral and Surgical Treatment in Peptic Ulcer, J. A. M. A. **108**:700 (Feb. 27) 1937.

ulcer and, second, to report on experimental work regarding the protective value of histidine against ulcer in dogs after the Mann-Williamson operation. Of a series of 291 patients with proved ulcer, 118 were treated with various forms of parenteral injections. The remainder were treated by orthodox diet-alkali measures and served as controls. Histidine, vaccine and emetine were the agents used for parenteral injection, and injections of distilled water were administered to a large group of controls (22 patients). From the results obtained Sandweiss concludes that in cases of chronic ulcer, parenteral therapy was of value when the patient failed to respond to diet-alkali management. In this group "parenteral therapy has its chief value as an additional method of treatment." He feels that the psychic factor is largely responsible for the favorable results when they occur. Injections of vaccine apparently were associated with the most satisfactory relief of symptoms, but all the agents employed were beneficial. It is of particular interest that practically 60 per cent of the patients receiving injections of distilled water were relieved of symptoms. The report on the protective value of histidine in experimental studies of ulcer in dogs is made by Sandweiss, Saltzstein and Glazer.[86] Of 14 dogs treated with histidine after the performance of a Mann-Williamson operation, only 1 failed to show a typical ulcer, and all the control animals showed similar lesions. These authors conclude that histidine had no effect in preventing the production of ulcer under the conditions of the experiment.

Clinical studies by Wilhelmj [87] and by Upham and Barowsky [88] support, in the main, the findings of Sandweiss. All agree that recurrences are in no way prevented by treatment with histidine. Upham and Barowsky, like Sandweiss, obtained striking relief of symptoms in a few cases by the use of injections of distilled water alone. A review of these and similar studies leads one to the conviction that histidine, as a therapeutic agent in the treatment of ulcer, is of only temporary value in a limited number of cases and that the favorable results obtained by its use are largely due to the psychotherapeutic effect which follows the parenteral injection of any nonspecific substance.

The medical treatment of peptic ulcer, aside from parenteral injections, has concerned itself with various forms of feeding and with

86. Sandweiss, D. J.; Saltzstein, H. C., and Glazer, W. S.: The Value of Histidine in the Prevention of Experimental Ulcer in the Dog, Am. J. Digest. Dis. & Nutrition **4**:20, 1937.

87. Wilhelmj, E. W.: Further Observations of the Histidine Treatment of Peptic Ulcer, Ann. Int. Med. **10**:1365, 1937.

88. Upham, R., and Barowsky, H.: A Clinical Investigation of Histidine Therapy in Cases of Peptic Ulcer, J. A. M. A. **109**:422 (Aug. 7) 1937.

newer preparations for the neutralization or adsorption of hydrochloric acid. An ingenious combination of frequent feedings of milk combined with alkali has been devised by Wosika,[89] who attempts to control gastric acidity by the use of tablets of alkalinized powdered skimmed milk. Comparative studies were made on a group of patients with successive regimens, consisting of (1) feedings of whole milk and cream alternating with those of standard Sippy powders, (2) feedings of milk and cream alternating with those of powdered whole milk mixed with the same powders and given as tablets, (3) the same feedings alternating with the taking of tablets of powdered whole milk and a mixture of calcium carbonate and sodium bicarbonate and (4) the same feeding alternating with the taking of tablets of powdered skimmed milk and a mixture of calcium and sodium bicarbonate. Apparently the fourth regimen consistently gave the best control of gastric acidity. For practical purposes the use of tablets composed of powdered milk and alkali provides convenience without excessive expense. To obviate the occasional danger of producing alkalosis, several preparations have been studied, all of which aim at neutralizing or adsorbing gastric acidity without altering the p_H of the blood. The effect of magnesium trisilicate has been studied by Mann.[90] Hourly feedings were combined with the administration on the half hour of 3.5 Gm. of the drug. Specimens of the stomach contents were tested at every first and third quarter hour, and practically no free acid could be demonstrated. In vitro studies indicated that acidity was controlled both by adsorption and by neutralization, in the ratio of 2 to 7. Levin[91] also advocates the use of synthetic hydrated magnesium trisilicate because of its prolonged adsorbent action.

Geréb and Körössy[92] discuss the use of a buffer preparation on the acidity and alkalinity of the stomach. They use a mixture of sodium biphosphate and sodium bisulfate in a ratio of 86 to 14. The preparation is given in doses of 1 Gm. at varying intervals. The result of the administration of this preparation is to acidify the urine. Relief was obtained in about 80 per cent of the cases in which it was tried. Laszlo,[93] also of Budapest, reports on the use of the product.

89. Wosika, P. H.: The Control of Gastric Acidity in Peptic Ulcer by Alkalinized Powdered Skimmed Milk Tablets, Am. J. M. Sc. **195**:676, 1938.

90. Mann, W. N.: Experiments on the Neutralization of Hydrochloric Acid by Magnesium Trisilicate, Guy's Hosp. Rep. **87**:151, 1937.

91. Levin, M. B.: Peptic Ulcer Therapy, Am. J. Digest. Dis. & Nutrition **4**: 574, 1937.

92. Geréb, I., and Körössy, F.: Therapy of Gastric Secretory Disturbances with Buffer Compounds, Gyógyászat **74**:146, 1934.

93. Laszlo, G.: Clinical Experiments with a Buffer That Normalizes the Hydrogen Ion Concentration of the Stomach, Rev. Gastroenterol. **4**:35, 1937.

He obtained amelioration of symptoms in three fourths of a series of 96 patients suffering from ulcer and other gastric disorders.

The search for the perfect antispasmodic still continues. Einhorn [94] substituted diphenylacetyldiethylaminoethanolester hydrochloride for belladonna in a small group of cases of gastrointestinal disorders. Toxic effects were not noted; and when distress or pain was not associated with an inflammatory reaction, satisfactory relief of symptoms was obtained. Several other investigators have made use of this new preparation, but as yet it has not been sufficiently tested to warrant further comment.

Two studies which yielded negative results are of interest. Warren, Friend and Emery [95] subjected 5 patients with ulcer, who volunteered for the experiment, to a diet similar to that used by Goldberger and Wheeler to produce pellagra. The basis for such an experiment lay in the fact that patients with pellagra frequently are found to have hypoacidity or anacidity. Two of the subjects followed the diet for an average of fifty-nine days and 1 for one hundred and twenty-five days. Gastric analyses performed every two or three weeks failed to indicate any change in gastric acidity, and it was concluded that such a dietary method of managing ulcer is obviously impracticable as well as unproductive of results. Emery and Schnitker [96] also administered bile to patients with peptic ulcer. The basis of such an experiment was the fact that diversion of bile from the duodenum in animals is an important detail in the experimental production of ulcer. A total of 40 patients were treated with desiccated ox bile over periods as long as two years. A satisfactory result occurred in only 52.5 per cent of the cases, a proportion that is not much better than that of spontaneous cures, as Emery aptly remarks. He also concludes that his results seem to rule out a disturbance in the biliary secretion as a cause of peptic ulcer in man.

An inconclusive article but one of possible physiologic interest is presented by Korbsch,[97] who treated 4 patients with gastric ulcer with injections of an estrogen substance. Excellent healing of the ulcer was observed gastroscopically after twenty-four, thirteen, twenty-

94. Einhorn, M.: The Use of a New Antispasmodic Drug in Gastro-enterology: A Preliminary Report, Am. J. Digest. Dis. & Nutrition **5**:121, 1938.

95. Warren, H. A.; Friend, D. A., and Emery, E. S., Jr.: The Treatment of Peptic Ulcer by the Diet of Goldberger and Wheeler, Am. J. Digest. Dis. & Nutrition **4**:495, 1937.

96. Emery, E. S., Jr., and Schnitker, M. A.: Peptic Ulcer: The Effect of the Administration of Bile on the Behavior of the Disease, Ann. Int. Med. **10**: 2007, 1937.

97. Korbsch, R.: Heilungen von Magenulzera durch Follikelhormon-Injektionen, Deutsche med. Wchnschr. **63**:599, 1937.

eight and sixteen days, respectively. One patient was said to have been resistant to other forms of therapy, and a second responded without the addition of dietary measures. Unfortunately the series is so small as to admit of no conclusions, particularly when it is remembered that spontaneous cure is extremely frequent. Favorable results have been reported for many types of parenteral therapy, and the comments of Sandweiss and others regarding injection methods of treatment must always be borne in mind in the evaluation of results such as are reported in this paper. Furthermore, another contribution by Sandweiss is pertinent in any consideration of the effect of hormones on the healing of ulcer. This article, by Sandweiss, Saltzstein and Farbman,[98] presents the results of injecting preparations of estrogenic substance (esterone, or theelin) and gonadotropic substance from the urine of pregnant women (antuitrin S) in dogs after the Mann-Williamson operation. The work was inspired by the clinical observation that pregnancy appears to have a beneficial effect on peptic ulcer. Twelve untreated animals all died of typical jejunal ulcer. Unlike the results claimed by Korbsch, all the 15 dogs that received injections of estrogenic substance died and showed ulcers similar to those noted in the controls and without any evidence of healing. Eight of a group of 15 animals treated with the gonadotropic substance which eventually died of inanition failed to show any evidence of ulcer formation. Seven died with jejunal ulcer, but 4 of these 7 showed microscopic evidence of healing. The author concludes, in a rather cautious manner, that the injection of large amounts of the gonadotropic substance may have been responsible for the favorable results.

The importance of considering psychologic factors in the treatment of peptic ulcer has been frequently noted. Two intelligent papers have been written on this aspect of the problem recently. Chappell, Stefano, Rogerson and Pike[99] carried out an interesting experiment on a group of patients with ulcer. In addition to routine dietary measures, evening lectures were given to these patients in order to provide a better understanding of such factors as worry, expenditure of effort, psychosomatic relation and self assurance. A control group were handled by dietary measures alone. Over a three year period the first group of patients responded to treatment better in every way than did the controls, and even those who suffered from relapses during this period were able to handle their symptoms more satisfactorily.

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98. Sandweiss, D. J.; Saltzstein, H. C., and Farbman, A.: The Prevention or Healing of Experimental Peptic Ulcer in Mann-Williamson Dogs with the Anterior Pituitary-Like Hormone (Antuitrin-S): A Preliminary Report, Am. J. Digest. Dis. & Nutrition **5**:24, 1938.

99. Chappell, M.N.; Stefano, J. J.; Rogerson, J. S., and Pike, F. H.: The Value of Group Psychological Procedures in the Treatment of Peptic Ulcer, Am. J. Digest. Dis. & Nutrition **3**:813, 1937.

The paper by Davies and Wilson [100] provides a convincing demonstration of the psychic element in the development of peptic ulcer. A series of 205 patients with ulcer were carefully examined psychologically, and it appeared that in 84 per cent of the cases the symptoms began shortly after some event affecting the patient's work, his finances or the health of his family. One hundred of these patients were compared with an equal number of patients with hernia, Culpin's system of group scoring being used. It was found that a significant majority of the patients with ulcer showed undue tension long before the symptoms of ulcer developed. The conclusion that successful therapy depends on attention to the "whole man," his work and his anxieties as well as his diet, if not original, is nevertheless of great importance, since even a superficial survey of the literature reveals innumerable conclusions as to the specificity or importance of various therapeutic maneuvers, with a fine disregard of the known history of this chronic disease.

The management of massive hemorrhage as an incident in the course of peptic ulcer is still a controversial matter. Conservative measures in the treatment of this emergency are undoubtedly indicated in the earlier decades of life. Mortality statistics are still confusing and in part depend on the character of the case under discussion or the type of treatment chosen. Meulengracht's [101] latest report on 368 medically treated patients with a mortality of only 1.3 per cent is amazing and indicates that the administration of a full diet to these patients must be considered seriously before what has seemed like a radical departure from accepted methods is discarded. Finsterer's [102] criticism that these represent cases of superficial gastric erosions and gastritis does not seem entirely tenable. Woldman's [103] small series of patients with massive hemorrhage treated with continuous aluminum hydroxide drip provides a new modification of the already known treatment with continuous milk drip. The fact that all 20 patients responded rapidly and satisfactorily to this treatment loses a little of its importance because of the failure of the author to give the nature of the underlying pathologic process in the different cases. Whether continuous drip methods are more efficacious than the method of Meulengracht will be determined only by prolonged use with large groups of patients. Opposed to such conservative measures are various surgeons

100. Davies, D. T., and Wilson, A. T. M.: Observations on the Life-History of a Chronic Peptic Ulcer, Lancet **2**:1353, 1937.

101. Meulengracht, E.: Weitere Erfahrungen über die Behandlung massiver Magenblutungen ohne Beschränkung der Nahrungszufuhr, München. med. Wchnschr. **84**:1565, 1937.

102. Finsterer, H.: Indikationsstellung zur operativen Behandlung der akuten schweren Magenblutung, Wien. med. Wchnschr. **88**:201, 1938.

103. Woldman, E. E.: The Treatment of Hematemesis and Melena by a Continuous Aluminum Hydroxide Drip, Am. J. M. Sc. **194**:333, 1937.

of known standing. The most radical of all the proponents of surgical treatment of bleeding ulcer is Finsterer.[102] In a recent summary of the subject he reiterates his conviction that gastric resection is the method of choice in practically all cases of massive gastric hemorrhage, including even known cases of cirrhosis, provided any gastric symptoms accompany the disease of the liver. Only if bleeding appears suddenly, without preceding symptoms, does he advise medical treatment. Between these two extremes lie the views of the majority of those interested in this difficult clinical problem. An excellent summary of the question is contained in a recent editorial in *The Journal of the American Medical Association*.[104] In all probability the crux of the situation is the age of the individual patient. With rare exceptions, patients under the age of 45 or 50 run an almost negligible risk when treated by careful medical procedures. After that age surgical intervention must not infrequently be considered as the logical form of treatment, the type of operation depending on the experience of the individual surgeon. Even in older patients conservative measures are usually indicated. When operation is involved, however, the decision to operate had best be made within the first forty-eight hours after bleeding, as suggested by Finsterer,[102] Allen [105] and others. Excellent reviews of the clinical aspects of gastric hemorrhage are presented by Jankelson and Segal,[106] by Blackford, Smith and Affleck [72] and others.

There is still no absolute agreement as to the proper surgical treatment for ulcer, even in the event of perforation. Numerous reports from various parts of the world are of interest, largely because of the differences of opinion that are shown. McCreery [107] expresses what is probably the point of view commonly held in this country in a report of 170 cases of perforated gastric or duodenal ulcer. He advocates simple closure in most instances, and this opinion is confirmed by Boneo and Ramirez,[108] of Buenos Aires, Chang,[69] of Peiping, and Lemberg [109] and Sosnyakov,[110] of Leningrad, to cite articles from widely scattered

104. The Bleeding Peptic Ulcer, editorial, J. A. M. A. **110**:1491 (April 30) 1938.

105. Allen, A. W.: Acute Massive Hemorrhage from the Upper Gastro-Intestinal Tract, with Special Reference to Peptic Ulcer, Surgery **2**:713, 1937.

106. Jankelson, I. R., and Segal, M. S.: Massive Hemorrhage from Peptic Ulcer, New England J. Med. **219**:3, 1938.

107. McCreery, J. A.: Perforated Gastric and Duodenal Ulcer, Ann. Surg. **107**: 350, 1938.

108. Boneo, G., and Ramirez, E. A.: Perforación gastroduodenal; observaciones de Guardia: 85 casos, Semana méd. **1**:104, 1938.

109. Lemberg, D. A.: Perforating Gastroduodenal Ulcers, Novy. khir. arkhiv. **37**:191, 1936.

110. Sosnyakov, N. G.: Gastroduodenal Perforation: One Hundred and Twenty-One Cases, Novy. khir. arkhiv. **39**:74, 1937.

points. Judin,[111] of Moscow, however, believes with other more radical surgeons that partial gastrectomy is the method of choice. Heim,[112] of Berlin, on the basis of 283 cases, comes to a similar conclusion. Judin's large series of 426 patients who were subjected to subtotal gastric resection, with a mortality of only 7.8 per cent, convinces one of his surgical skill, however, rather than of the soundness of his judgment in choosing such a radical procedure.

There is a similar difference of opinion as to the surgical method of choice in uncomplicated ulcer. Articles by Abell [113] and Walters [114] are representative of those advocating the simplest type of operation for duodenal ulcer, namely gastroenterostomy. Subtotal gastrectomy as a routine procedure for duodenal and gastric ulcer has met with the approval of many continental surgeons, following the work of Finsterer and Hoffmeister. This more radical procedure is chosen by many, and articles by Manizade,[115] Hustinx,[116] Mouchet [117] and Neuman,[118] for example, proclaim the benefits of using this method. The middle of the road opinion is well summarized in an article by Marshall and Kiefer,[119] who point out correctly that most cases of ulcer offer primarily medical problems; in the event that surgical intervention is necessary, the problem is always an individual one, and the type of operative approach must be decided by balancing the probable risks against the probable benefits. Finsterer [120] reports a series of 200 unusual cases of jejunal ulcer, with a mortality of only 11.1 per cent after radical operation in 180 cases of uncomplicated jejunal ulcer. The mortality for the entire series was 15.3 per cent.

111. Judin, S. S.: Partial Gastrectomy in Acute Perforated Peptic Ulcer, Surg., Gynec. & Obst. **64**:63, 1937.

112. Heim, W.: Nachuntersuchungen operierter perforierter Magen- und Zwölffingerdarmgeschwüre, Deutsche med. Wchnschr. **63**:1321, 1937.

113. Abell, I.: The Surgical Treatment of Peptic Ulcer, Ann. Int. Med. **11**: 762, 1937.

114. Walters, W.: Should Gastric Resection Be Done for Duodenal Ulcer? Surgery **2**:759, 1937.

115. Manizade, M. D.: Zur Frage der Anämie nach Magenresektion, Wien. klin. Wchnschr. **50**:1455, 1937.

116. Hustinx, E.: Le traitement de l'ulcère du duodénum par la résection gastro-duodénale: sa technique, ses résultats immédiats et éloignés, Arch. franco-belges de chir. **35**:305, 1936.

117. Mouchet, A.: Quelques reflexions sur la gastrectomie dans l'ulcère gastro-duodénale, Paris méd. **2**:81, 1937.

118. Neuman, F.: Le traitement des ulcères gastriques et duodénaux par la gastrectomie, Bull. Acad. roy. de méd. de Belgique **1**:417, 1936.

119. Marshall, S. F., and Kiefer, E. D.: Partial Gastrectomy for Gastric or Duodenal Ulcer, J. A. M. A. **109**:1341 (Oct. 23) 1937.

120. Finsterer, H.: Erfahrungen bei über 200 selbst ausgeführten Radikaloperationen wegen Ulcus pepticum jejuni, Arch. f. klin. Chir. **189**:597, 1937.

It is of interest that serious anemia is of infrequent occurrence after subtotal gastrectomy. Manizade [115] made a study of 40 patients who were examined from five to twelve years after operation. In all cases, extensive resection, involving two thirds of the stomach, had been performed. Examination of the blood showed that in 36 of the 40 cases the red blood cell count was over 4,500,000 and the hemoglobin value over 80 per cent (Sahli). Two patients showed a slight degree of normochromic anemia. Two patients, or 5 per cent of the entire series, were found to have hyperchromic anemia, with a red blood cell count in the vicinity of 2,000,000. One of these patients, prior to operation, showed an abnormal blood picture, suggesting an early stage of pernicious anemia, and gave the history that her mother had died of pernicious anemia. These findings are entirely consistent with comments made by other investigators who have followed the behavior of the blood after radical gastric operations. It is obvious that the danger of the development of a serious form of anemia after the removal of a large portion of the stomach is not important. Factors predisposing to the development of such a condition may exist before operation, and gastric resection rarely initiates the appearance of primary hyperchromic anemia. Blood regeneration after hemorrhage from an ulcer was considered by Schiødt,[121] who found that age, sex and the form of bleeding (melena or hematemesis) made little or no difference in the rate of recovery from the loss of blood. He did find, however, that regeneration was much slower when the patient was treated with a restricted diet, such as the Sippy regimen, than with a full diet, as suggested by Meulengracht. With a Meulengracht regimen he found that the lower the initial blood level after hemorrhage, the more rapid the response to therapy; whereas the converse was true for patients with a restricted dietary intake. Transfusion obviously was necessary in certain cases but did not hasten blood regeneration—a point that has frequently been noted.

A discussion of the subject of gastrojejunocolic fistula by Rife [122] presents no new information concerning one of the complications of gastric operations but gives a complete and thoughtful review of the subject.

Few additions have been made to the already existing mass of information on carcinoma of the stomach. Castleman [123] contributes

121. Schiødt, E.: The Influence of Sex, Age, Form of Hemorrhage, Treatment and Complications on Erythrocyte Regeneration After Hematemesis and Melena from Peptic Ulcer, Am. J. M. Sc. **193**:327, 1937.

122. Rife, C. S.: Gastrojejunocolic Fistula, Am. J. Surg. **40**:73, 1938.

123. Castleman, B.: Extension of Gastric Carcinoma into the Duodenum, Ann. Surg. **103**:348, 1936.

the important pathologic observation that not infrequently cancer of the lower end of the stomach extends beyond the pylorus into the duodenum. Such a finding is an indication that ample resection of the first portion of the duodenum, whenever possible should accompany resection of the gastric neoplasm. Balfour [124] has reviewed the subject, basing his observations on a series of 4,793 patients operated on at the Mayo Clinic. In 2,112 cases the growth was removed as a palliative measure or in the hope of a cure, which a mortality of 13.9 per cent. Several points of interest are mentioned. For the most part, the percentage of five-year survivals was larger for the older patients and for those who had a longer story of preoperative symptoms. The nearer the growth was located to the pylorus, the more difficult it was to obtain a successful surgical result. Patients with a carcinomatous growth graded 1 or 2 showed 63 per cent survival after five years and 55 per cent survival after ten years; those with growths graded 3 or 4 showed only 20 per cent survival at the end of the five year period. These statistics offer rather convincing evidence that radical surgical treatment is justified, even in what seem to be rather hopeless cases of gastric cancer.

Shiflett [125] presents a review of diverticulum of the stomach and considers that it may be of definite clinical significance after other conditions have been ruled out as potential factors in causing the patient's symptoms. In a series of 786 roentgenograms of the stomach and 887 similar studies of the colon, the occurrence of diverticula was as follows: colon, 4.96 per cent; duodenum, 3.74 per cent; esophagus, 0.79 per cent; stomach, 0.65 per cent, and small bowel, 1 case. He reviews his own 5 cases and 38 reported in the literature; one third of the patients had definite symptoms of burning or vomited.

Little new has been contributed in the way of roentgenologic studies of peptic ulcer. However, an article by Hampton [126] presents a satisfactory technic for the demonstration of a dangerously bleeding ulcer. Whenever compression or palpation is contraindicated or impossible, it is now possible by this method to make a profile, relief and double contrast examination of the posterior wall of the stomach, the pyloric valve and the posterior wall of the duodenum. The examination can be carried out when there is active bleeding with little if any additional risk and can thus provide information that is frequently essential to

124. Balfour, D. C.: Factors of Significance in the Prognosis of Cancer of the Stomach, Ann. Surg. **105**:733, 1937.

125. Shiflett, E. L.: Diverticula of the Stomach, Am. J. Roentgenol. **38**:280, 1937.

126. Hampton, A. O.: A Safe Method for the Roentgen Demonstration of Bleeding Duodenal Ulcers, Am. J. Roentgenol. **38**:565, 1937.

the proper planning of therapeutic measures. The report of Unger and Poppel [127] calls attention to an error in roentgenographic interpretation that may lead to improper steps in the treatment of a known ulcer. They report on a patient with gastric ulcer who was operated on because a persistent niche was demonstrated roentgenographically, despite symptomatic cure after five weeks of treatment. At operation the ulcer was found to be completely healed. The conclusion that roentgenologic findings are in themselves insufficient evidence on which to base a therapeutic decision is obvious, but the warning is timely. Bignami [128] presents a rather interesting review of the subject of extrabulbar duodenal ulcer. Among 400 cases of duodenal ulcer the author found 18 cases in which there was extrabulbar location. From his own experience and from the findings of others, the writer believes that this type of ulcer occurs most frequently in the convexity of the duodenal loop and in the suprapapillary region. He considers that the demonstration of a niche at roentgen examination is the only infallible evidence of an extrabulbar ulcer, although with modern relief methods it is probably true that the demonstration of a crater is of equal diagnostic importance. The chief value of the article is that it stresses the occurrence of a lesion that is all too frequently missed by routine roentgenographic methods of study.

GASTROSCOPY

The increasing number of articles on this subject is convincing evidence of the interest as well as the importance of gastroscopic examination as a diagnostic procedure. In this country, in particular, the enthusiastic reception of a new diagnostic aid is the undoubted forerunner of a host of articles, few of which will be written in a sufficiently critical spirit to warrant their appearance. It will be necessary for some time to warn against undue enthusiasm and against conclusions drawn from improperly controlled material. The wise counsel of Henning and Schindler must be repeated many times before a satisfactory correlation is made between gastroscopic findings and clinical symptoms. Normal variations, which are extremely wide and still are not fully appreciated, must be conscientiously studied and classified before an adequate understanding is obtained of the many changes in the appearance of the gastric mucosa. There is little question, however, that such understanding will come and that gastroscopic examination will provide increasingly valuable assistance in the study of gastric disease and gastric physiology.

127. Unger, A. S., and Poppel, M. H.: Healing of Gastric Ulcer with Persistence of Niche Roentgenographically, Am. J. Roentgenol. **39**:592, 1938.

128. Bignami, G.: Rilievi sopra un nuovo gruppo di osservazioni di ulcera del duodeno in sede extrabulbare, Boll. d. Soc. med.-chir., Pavia **51**:401, 1937.

The outstanding work on gastroscopy during the period of this review is the book by Schindler.[129] A detailed review is unnecessary at this time, but the volume has almost universally received favorable comment. Schindler discusses the history of the subject with anatomic notes, the mechanical problems of technic and orientation, the appearance of the normal stomach and the appearance in cases of functional and pathologic disturbances. He repeatedly emphasizes the most important point, that gastroscopic examination is an adjunct to roentgen examination and that both methods are essential to an accurate diagnosis of gastric disorders. Ninety-six excellent color plates add greatly to the usefulness of this important volume.

Schindler[130] calls attention to the type of tip to be used on the flexible gastroscope. With other workers, he believes that the original sponge tip produces too much friction and may result in perforation of the gastric wall. The rubber finger tip appears to be preferable, in that it directs the instrument more satisfactorily; and it is safer, because it produces no friction. Korbsch[131] prefers his new small rigid gastroscope, with a diameter of only 6 to 7 mm., to the Wolf-Schindler instrument. Halmős[132] agrees in choosing this instrument, which gives a smaller picture but a larger field. He claims to have noted finer details of gastric markings, small hemorrhages and early mucosal hypertrophy that could not be observed with the flexible scope. This is not in agreement with the opinion of nearly all other observers, who believe that the flexible Wolf-Schindler instrument is safer and more satisfactory. Kirihara and his co-workers[133] have attempted to improve on the Wolf-Schindler gastroscope by adding a mechanism by which the tip can be bent at will. The mechanism is described and it is possible that the authors' claims will be justified. They state that with this modification they can obtain a much better view of the pyloric end of the stomach.

Contrary to the experience of most observers, Borland[134] has found that there are no true "blind spots" and thinks that by proper manipu-

129. Schindler, R.: Gastroscopy: The Endoscopic Study of Gastric Pathology, Chicago, University of Chicago Press, 1937.

130. Schindler, R., and Renshaw, J. F.: Experimental Study with Certain Tips Used on the Wolf-Schindler Flexible Gastroscope, Am. J. Digest. Dis. & Nutrition **3**:747, 1936.

131. Korbsch, R., cited by Halmős.[132]

132. Halmős, R.: Die Magenspiegelung mit den dünnkalibrigen Instrumenten nach Korbsch, Med. Klin. **33**:702, 1937.

133. Kirihara, S.; Nakayama, H.; Saloh, Y.; Konda, Y., and Ito, I.: Japanese Improved Flexible Gastroscope, Nagoya J. M. Sc. **11**:1, 1937.

134. Borland, J. L.: Present Status of Flexible Tube Gastroscopy, South. M. J. **30**:310, 1937.

lation of the instrument, by changing the position of the patient and by observing the peristaltic wave, all portions of the stomach can be brought into view. His suggestions as to gastroscopic technic are of interest, but it must be admitted that a satisfactory examination of certain parts of the stomach in particular cases is extremely difficult. These portions are notably the lesser curvature near the pylorus in a J-shaped stomach; the greater curvature, at a point where the tip of gastroscope impinges, and occasionally high up on the posterior wall, where the objective lens is in immediate contact with the gastric mucosa.

A point of importance is made by Schindler [135] in an article on the anatomy of the stomach. He calls attention to the division of the interior of the stomach into the body and the antrum, distinctly separated by the characteristic cordlike muscular antral sphincter. This is an important gastroscopic landmark and is formed, he believes, by a circular contraction of the muscularis propria, which is crossed by oblique folds of mucosa. He also calls attention to the mucosal folds as observed gastroscopically. These are most marked on the posterior wall, usually absent on the lesser curvature and always absent from the antrum. They do not seem to correspond completely with the roentgenographic relief markings.

Studies of gastric physiology as observed through the gastroscope are few. Brühl [136] has studied the effect of externally applied heat and cold on the appearance of the stomach. The application of a hot water bottle to the epigastrium always increased peristaltic activity and usually caused marked reddening of the gastric mucosa. Opposite effects were noted with the application of cold. These findings are entirely in accord with the studies on gastric motility previously alluded to. In 1,700 examinations Chevallier, Moutier and Debrey [137] observed 4 instances of sudden changes in the color of the gastric mucosa, which they can explain only on the basis of a vasomotor disturbance. They believe that these changes are not due to the effect of drugs or the presence of the instrument. The changes in color were striking.

The clinical value of gastroscopic examination is undoubtedly greatest in its fairly exact determination of the source and the character of gastric bleeding. Chevallier and Moutier [138] have made an

135. Schindler, R.: Gastroscopic Observation Concerned with the Gross Anatomy of the Stomach, Am. J. Digest. Dis. & Nutrition **3**:149, 1936.

136. Brühl, W.: Gastroskopische Untersuchungen über die Wirkung thermischer Hautreize auf den Magen, Deutsche med. Wchnschr. **63**:129, 1937.

137. Chevallier, P.; Moutier, F., and Debrey, C.: Perturbations vasomotrices segmentaires constatées à l'endoscopie gastrique, Arch. d. mal. de l'app. digestif **27**:1042, 1937.

138. Chevallier, P., and Moutier, F.: Les hémorragies gastriques et leur contrôle endoscopique, Presse méd. **44**:1814, 1936.

excellent report on hemorrhage from the stomach. They point out that the normal gastric mucosa does not bleed on the introduction of the gastroscope. Artificial hemorrhages may be due to abnormal fragility of the mucosa, a point carefully noted by Baumel,[139] who calls attention to the fragility of the mucosa in superficial gastritis and its tendency to bleed easily, especially on the lesser curvature and on the posterior wall near the cardia. Chevallier and Moutier comment on the fact that gastric purpura may exist with or without external manifestations. Mucosal eruptions resemble the cutaneous lesions, and macular ecchymoses may be found in all parts of the stomach. Gastric hematoma is rare; but 1 case was noted (a case of splenomegaly). Varicose veins have also been observed in a stomach with an atrophic mucosa, the patient in this instance having had two or three hemorrhages a year. Gastroscopic examination showed the frequency of ulcer which is silent clinically and roentgenologically but which is capable of bleeding. Such a hemorrhagic lesion is most frequently encountered on the lesser curvature at the angle of the stomach. Chevallier [140] has also expressed the conviction that ulcer is not a frequent cause of bleeding. He thinks that the usual cause is found in a fleeting hemorrhagic lesion which may be near to or at a distance from an actual peptic ulcer. In other words, he feels that even though an ulcer is present at the time of a gastric hemorrhage, it may well be inactive and the bleeding may be due to an area of active gastritis. Such an area may present a localized spot with fine ecchymotic speckling, sometimes hardly discernible. He believes that bleeding from cancer is usually due to concomitant gastritis of the hemorrhagic or erosive type. He finds submucosal hemorrhage fairly frequent in hepatic insufficiency but rare in early cirrhosis and exceptional in advanced cirrhosis. In certain cases of cholecystitis and chronic appendicitis accompanied by hematemesis, gastroscopic examination has demonstrated discrete and fleeting changes in the gastric mucosa, which, Chevallier is sure, form the anatomicopathologic basis of the bleeding. Granted the correctness of the underlying diagnosis, these findings are of interest in relation to the cases of disease of the gallbladder with hematemesis reported a few years ago by White. Benedict [141] has also emphasized the clinical importance of gastritis as a cause of massive bleeding from the stomach. Although

139. Baumel, J.: La gastroscopie en pathologie gastrique: gastrites—ulcus—diverticules—cancer—tumeurs bénignes, Bronchoscop., œsophagoscop. et gastroscop., April 1937, p. 105.

140. Chevallier, R.: Les hémorragies gastriques: Etude gastroscopique, Lyon méd. **159**:3, 1937.

141. Benedict, E. B.: Hemorrhage from Gastritis: A Gastroscopic Study, Am. J. Digest. Dis. & Nutrition **4**:657, 1937.

such an observation is not new, it has received insufficient notice until recently. The importance of his observations lies in the fact that frequently a gastric hemorrhage of alarming proportions may occur with no clinical or roentgenographic indication of its source. He presents gastroscopic and roentgenographic studies of 20 cases of acute or chronic gastritis with hemorrhage. The only likely and demonstrable source of the bleeding in these cases was found gastroscopically to be superficial or hypertrophic gastritis, often with one or more erosions in the gastric mucosa. In these cases the excessive use of alcohol seemed to be a frequent factor in the precipitation of the hemorrhage.

As clearly emphasized by Henning and Schindler, the exact diagnosis of gastritis as a cause of clinical symptoms demands long experience in gastroscopic studies and excellent clinical judgment. The classification of this condition is still far from clear, but to most observers Schindler's classification appears to be the simplest and therefore the most practicable. Certainly at present too detailed a nomenclature will end only in confusion, although it must be admitted that any classification may at times be entirely unsatisfactory. Schindler,[142] in attempting to correlate the histologic and gastroscopic findings in chronic gastritis, concludes that a positive microscopic picture does not prove the existence of clinical "disease" of the stomach. Almost every adult shows some interstitial changes in the stomach as compared with the histologic picture in the newborn. Obviously, prolonged observation is needed to harmonize anatomic and gastroscopic findings in a disease the clinical significance of which is imperfectly understood. On the other hand, as indicated in the careful report of Schloss, Ettinger and Pratt,[143] gastroscopic study frequently provides an explanation for symptoms in certain cases in which the condition has been diagnosed as normal or psychoneurotic by the usual procedures. Although the subject is far from new, the report by Ansprenger and Kirklin [144] provides an excellent discussion of the limitations of the roentgenologist in attempting to make a diagnosis of gastritis. Serious changes seen gastroscopically may completely escape roentgenographic detection. In only a small proportion of cases of gastritis can the diagnosis be made by the roentgenologist. Mucosal atrophy cannot be seen roentgenographically. The most important and most frequent roentgenologic

142. Schindler, R.: Relationship of Histologic and Gastroscopic Findings in the Diagnosis of Chronic Gastritis, Am. J. Digest. Dis. & Nutrition **3**:153, 1937.

143. Schloss, J.: Ettinger, A., and Pratt, J. J.: Diagnosis of Diseases of the Stomach by Gastroscopic and X-Ray Relief Studies, Am. J. M. Sc. **193**:171, 1937.

144. Ansprenger, A., and Kirklin, B. R.: Roentgenologic Aspects of Chronic Gastritis: Critical Analysis, Am. J. Roentgenol. **38**:533, 1937.

sign of gastritis is the presence of localized rigid, irregular, hypertrophic mucosal folds. Wartlike granulations, mucosal erosions that can be demonstrated *en face* and pseudopolypous formations are so infrequently demonstrable that they are of relatively little importance in the diagnosis of gastritis. Tangential projections on or near the lesser curvature, such as have been described, can be observed more frequently. When found they constitute absolute proof of the presence of ulcerous gastritis. Indirect signs must be interpreted with great caution and are significant only when associated with more definite findings. In addition to these comments of Ansprenger and Kirklin, one may say that even when the roentgenographic diagnosis of gastritis is correct, it cannot be as complete as that made with the aid of the gastroscope. Negative roentgenographic findings are of no value in the making of this particular diagnosis.

Schindler, Ortmayer and Renshaw [145] have attempted to classify the symptoms of chronic gastritis. They state that 50 per cent of the patients with superficial gastritis show periodic distress and 30 per cent constant distress, usually epigastric burning, gnawing, dull pressure or pain. Two thirds of these patients obtain relief with alkali and one third with food. In hypertrophic gastritis, half the patients also show periodic distress, with severe pain in 25 per cent and dull burning or gnawing in the remainder, usually one to three hours after meals. In 50 per cent of such cases, food or alkali gives relief. The predominance of males with hypertrophic gastritis is striking, the ratio being 22 to 1 in the cases studied. Antral gastritis was noted only twice. No correspondence was noted between the extent and severity of the gastritis observed gastroscopically and the severity of the symptoms. Schindler [146] reports an unusual case of hypertrophic gastritis with ulceration in which roentgen therapy was given. This patient was observed over a period of twelve years. The diagnosis could be made only by gastroscopic study, as roentgenographic relief study did not demonstrate marked changes in the mucosa. A gastroscopic study was made sixty-five times in this case. Ulceration and pain were present, in spite of all the usual methods of treatment. Although marked gastritic changes were present, with superficial ulceration, true peptic ulcer did not develop. High voltage roentgen therapy caused severe, acute, purulent gastritis, with subsequent regeneration of an essentially normal mucosal membrane. It is of interest to note, however, that one year later atrophic gastritis developed. At present it is probable that

145. Schindler, R.; Ortmayer, M., and Renshaw, J. F.: Chronic Gastritis, J. A. M. A. **108**:465 (Feb. 6) 1937.

146. Schindler, R.: Chronic Hyperthrophic Ulcerative Gastritis Treated by Coutard's Method of Roentgen Therapy, Am. J. Digest. Dis. & Nutrition **3**:751, 1937.

no one is in a position to evaluate the relation between chronic gastritis and peptic ulcer, and any conclusions as to whether or not gastritis is the underlying cause of ulcer are purely speculative. Einhorn,[147] in a clinical study, says he believes that ulcer is not the result of gastritis. His article loses much of its force since his conclusions are not based on gastroscopic evidence, but his argument that the acidity in chronic gastritis is low, in contrast to the high acidity in peptic ulcer, is probably sound. Taylor [148] in a gastroscopic study, comes to the opposite conclusion. In discussing the question of postoperative gastritis he assumes that some of the inflammatory process was present before the operation and was therefore the cause of the peptic ulcer.

In this connection there are numerous studies of the common condition of postoperative gastritis. Such observations are gradually accumulating evidence that is important as regards the indications for surgical treatment of ulcer and as an aid to the explanation of many postoperative symptoms. Schindler and Giere [149] discuss the relation of the gastroscopic findings to gastric operations and emphasize the importance of gastroscopic study in differentiating between benign and malignant disease, in determining the operability of carcinoma and in making an early diagnosis of carcinoma. Although they state that postoperatively the stoma can usually be seen, they point out the difficulties frequently encountered. A relatively normal gastric mucosa is seen in only about 10 per cent of cases postoperatively. Among the postoperative gastroscopic findings, chronic gastritis is most common; but recurrent ulcer, jejunal ulcer, hemorrhagic erosions and silk sutures which have cut through the mucosa are also found. In this article Schindler again calls attention to the pylorus-like rhythmic activity of the artificial stoma. Carey [150] has contributed an article on the postoperative appearance of the stomach; as a result of his findings he believes that every patient who is to be operated on for peptic ulcer should have a preliminary gastroscopic study, as frequently the symptoms are due to hypertrophic gastritis. In such cases roentgen examination may show only one of the numerous ulcers and erosions that are actually present. This concept is undoubtedly correct. The demonstration of multiple erosions or ulcers or of severe gastritis may be of great importance in deciding on the type of surgical procedure to be

147. Einhorn, M.: Quel est le rôle de la gastrite chronique dans l'étiologie de l'ulcère peptique? Bull. Acad. de méd. de Roumanie **2**:165, 1937.

148. Taylor, H.: History, Technic and Clinical Value of Gastroscopy, with Report on Sixty Cases, Brit. J. Surg. **24**:469, 1937.

149. Schindler, R., and Giere, N.: Gastric Surgery and Gastroscopy, Arch. Surg. **35**:712 (Oct.) 1937.

150. Carey, J. B.: Gastroscopic Observations of the Postoperative Stomach, Surg., Gynec. & Obst. **65**:447, 1937.

adopted or may even show the process to be so extensive that medical treatment should be given further trial. Carey believes that a stomal ulcer is much more readily seen gastroscopically than roentgenographically, although a jejunal ulcer is obviously more readily demonstrated roentgenographically. Carey's article is one of the best of several emphasizing the importance of studies of the preoperative and postoperative condition, and he as well as others points out the excellent opportunity that exists for obtaining direct visual evidence of the efficacy of various forms of therapy.

The problem of gastric ulcer obviously has received the careful attention of numerous observers. As in many aspects of gastroscopic study, little that is absolutely new has been added, but much interesting material has been accumulated. Schloss, Ettinger and Pratt [143] observed a gastric ulcer in 18 cases, in only 11 of which it was visible roentgenographically. These were true peptic ulcers and not superficial erosions. This has been noted by other observers, but it should also be noted that the converse is true and that both methods of examination should always be employed. Baumel points out that an old ulcer during a period of quiescence is less red than a new active ulcer and that the periulcerous base of the old ulcer is smaller, showing a tendency to equalization of the colors of the diseased and of the healthy parts of the mucosa. During the evolution of the ulcer toward healing, the defect becomes whiter than the surrounding tissue and lustrous. He, as have others, points out the value of repeated observations in an evaluation of the effect of various forms of therapy. Such a study was made by Fröhlich [151] during the course of treatment of chronic gastritis with a 4 per cent solution of levohistidine monohydrochloride in an isotonic medium. Repeated gastroscopic study showed progressive improvement in the appearance of the mucosa, with the disappearance of erosions and edematous areas. His series included only 5 cases, however, a group that is too small to warrant any conclusions.

With regard to gastric cancer, few hold the extreme view of Schindler that malignant lesions can be diagnosed with certainty gastroscopically, although all agree that valuable diagnostic aid can be obtained in this way. Baumel [139] believes that the first suspicious gastroscopic sign of cancer is the rigid state of the wall of the stomach even in the absence of any visible lesion. The second important sign is the leukoplakic appearance. After the tumor has developed the malignant ulcer presents an irregular, jagged outline, with edges that are less perpendicular than those of a benign ulcer and often are covered with grayish black material. The mucosa surrounding a malignant ulcer is paler than

151. Fröhlich, E.: Gastroskopische Befunde bei chronischer Gastritis nach Larostidin-Kur, Med. Klin. **33**:933, 1937.

that surrounding a benign ulcer. Baumel feels that the gastroscopic diagnosis of infiltrating cancer of the antrum and pylorus is possible before there are clinical or roentgenographic signs. In such cases the mucosal folds entirely disappear, and the area affected is boardlike and immobile, without any evidence of peristalsis. He recognizes, as do others, the difficulty of differentiating hypertrophic gastritis from pseudolipomatous or polypoid tumor. Malignant polyps are found to bleed more easily than benign polyps, at the least contact with the gastroscope. Kark [152] reports a case of aplastic anemia with secondary carcinoma following atrophic gastritis in which autopsy showed the stomach to be lined with "thin smooth mucosa devoid of rugae or relief of any sort," except in the pyloric antrum, where there was a small fungating adenocarcinoma. He estimated that the growth was probably of only a few weeks' duration but that the gastritis was clearly of several years' duration. It is pertinent to call attention to such cases in order to emphasize the probable importance of atrophic gastritis in its relation to malignant disease. It is probably a fact that gastric neoplasm arises more frequently from an atrophic mucosa than from an apparently normal one.

Benedict,[153] in reviewing the results of 456 gastroscopic examinations, again calls attention to the fact that in the so-called atrophic gastritis of pernicious anemia, liver therapy rapidly improves the condition of the gastric mucosa. Chevallier and Moutier [154] have also studied the gastroscopic aspect of repair in atrophic gastritis in the anemias, with particular reference to hypochromic and pernicious anemia. They have confirmed the original observations of Jones, Benedict and Hampton in regard to pernicious anemia and, in addition, in regard to the changes in the appearance of the mucous membrane; they comment on the diminished fragility of the mucosa and the apparent diminution in the secretion of mucus after specific treatment. These observers have noted an improvement in the gastric mucosa within three weeks after the initiation of liver therapy, with apparent complete restoration to normal of certain areas in three months. The formation of new areas of mucosa is indicated by the appearance of tiny ruby-colored points which can be readily observed. With regard to the

152. Kark, R. M.: Two Cases of Aplastic Anaemia, One with Secondary Haemochromatosis Following Two Hundred and Ninety Transfusions in Nine Years, the Other with Secondary Carcinoma of the Stomach, Guy's Hosp. Rep. **87**:343, 1937.

153. Benedict, E. B.: The Importance of Gastroscopy in Surgical Diagnosis, Am. J. Surg. **40**:5, 1938.

154. Chevallier, P., and Moutier, F.: Aspect gastroscopique de la réparation des gastrites atrophiques dans les anémies et les metanémies, Arch. d. mal. de l'app. digestif **27**:437, 1937.

atrophy of the gastric mucosa in pernicious anemia, it should be pointed out that it is entirely probable that the process is not true atrophic gastritis but rather an atrophic process secondary to what is generally accepted as a deficiency disease.

The difficulty of differentiation between acute gastritis and perforated peptic ulcer is discussed by Klostermeyer.[155] He points out that such severe forms of gastritis are found more frequently in patients with long-standing gastric complaints due to gastritis. He reports the findings in 80 such cases in which operation was performed because of the impossibility of making a diagnosis. At operation no perforation was seen but there was acute gastritis, with fresh inflammatory erosions in the resected specimens. Five such cases occurred in the author's experience in one year in the Hamburg Clinic. One is somewhat inclined to wonder at the necessity for gastrectomy in such instances, but it cannot be denied that the observations are of clinical interest.

One case reported by Touraine, Moutier and Soulignac[156] is of interest because of a rare finding. The 70 year old patient had typical cutaneous lesions of mycosis fungoides, with atrophic gastritis, splenomegaly and marked eosinophilia. Gastric lesions are rare in mycosis fungoides; when they occur they usually take the form of mucosal tumors resembling tumors of the skin. This is the first report of gastric atrophy in this disease, but it must be admitted that the findings may have been only coincidental.

THE SMALL INTESTINE

Interest in the clinical and physiologic aspects of disturbances of the small intestine has increased greatly in recent years. With the addition of newer methods for making physiologic studies, real contributions are constantly being added to the knowledge of this rather blind portion of the digestive tract.

An ingenious attempt has been made by Irving, McSwiney and Suffolk[157] to isolate functionally the afferent fibers from the stomach and small intestine. Dilatation of the pupils of the cat anesthetized with chloralose (a compound of chloral hydrate and dextrose) and reflex changes in the blood pressure in a similar preparation were utilized as indexes of visceral afferent stimulation. The gastric and duodenal

155. Klostermeyer, W.: Die akute Gastritis unter den Erscheinungen einer Ulkus-Perforation, München. med. Wchnschr. **84**:695, 1937.

156. Touraine, A.: Moutier, F., and Soulignac: Mycosis fongoïde avec gastrite atrophique, splénomégalie et forte éosinophilie sanguine, Bull. Soc. franç. de dermat. et syph. **44**:417, 1937.

157. Irving, J. T.; McSwiney, B. A., and Suffolk, S. F.: Afferent Fibers from Stomach and Small Intestine, J. Physiol. **89**:407, 1937.

mesenteries are innervated by the vagus and splanchnic nerves and are sensitive to traction. The jejunal mesentery seems to be supplied by the splanchnic nerves. The body of the stomach, pyloric antrum and sphincter were sensitive to distention and were innervated with afferent fibers to the vagus and sympathetic nerves. The lowest threshold to distention was obtained from the pyloric sphincter. The right and left splanchnic nerves supply afferent fibers to the stomach and duodenum. The jejunum and ileum are much less sensitive to distention than are the stomach and duodenum. The right and left splanchnic nerves appear to be the main afferent pathway from these regions.

The effect of vitamin A deficiency on the gastrointestinal tract was studied in monkeys by Verder and Petran.[158] The gross structural changes resulting from vitamin A deficiency were hyperplasia of the mesenteric lymph nodes and hyperemia of the intestinal mucosa. These were definite in the small bowel but not striking in the colon.

Yoder [159] found evidence in rachitic rats that vitamin D in optimal amounts increases intestinal motility by about 25 per cent. By inference one draws the conclusion that in vitamin D deficiency, motility is distinctly reduced. The same author [160] also studied the effect of vitamin D therapy on intestinal reduction of iron. Previous experiments on rachitic rats had shown that iron passes through the digestive tract in these animals in a less reduced state. Intestinal reduction of iron rose from a low value for the ileum to relatively high values for the cecum and colon in rachitic rats. Vitamin D therapy had little effect on the reduction of iron in the ileum but brought about a definitely decreased reduction in the cecum, colon and feces.

Beazell, Schmidt and Ivy [161] have carried out experiments on the effect of heat on the flow of blood and lymph in the intestinal tract. Heat was applied to the lumen of isolated segments of the small intestine and colon, with temperatures ranging from 52.2 to 57.7 C. It was shown that the flow of blood locally was markedly increased, even to the extent of being quadrupled, without effect on the rate of flow of lacteal lymph. Coincident with the increase in blood flow was an increase in the secretion of succus entericus. As long as there was no interference with the blood supply of the bowel by overdistention or contraction, the viscus might be heated to 52.2 C. Temperatures over

158. Verder, E., and Petran, E.: Vitamin A Deficiency in Rhesus Monkey: Studies on Gastro-Intestinal Tract, Blood and Nervous Symptoms, J. Infect. Dis. **60**:193, 1937.

159. Yoder, L.: Effect of Vitamin D on Intestinal Atony of Rickets, Am. J. Digest. Dis. & Nutrition **3**:828, 1938.

160. Yoder, L.: Effect of Vitamin D on Intestinal Iron Reduction, Am. J. Digest. Dis. & Nutrition **3**:829, 1937.

161. Beazell, J. M.; Schmidt, C. R., and Ivy, A. C.: Effect of Meat on Blood and Lymph Flow from Gastro-Intestinal Tract, Am. J. Physiol. **119**:197, 1937.

this, however, were found to be dangerous, the injury resulting in a diminished flow of blood and an increased flow of lymph.

Studies by Robertson [162] on intestinal stasis due to a low intake of minerals showed that in children, diets low in calcium and potassium are constipating and may cause stasis in the appendix. When given a barium sulfate meal, 6 of 18 children with diets low in calcium and phosphorus retained the barium in the appendix for from four to twenty-one days. These same children when receiving normal diets showed no barium in the appendix for more than one day.

Alvarez [163] describes a simple apparatus for the study of intestinal peristalsis. By means of this apparatus it is possible to squirt with measured force a measured amount of fluid into the duodenum. In normal rabbits such stimulation usually produced a peristaltic rush. This was studied by a new enterograph, which was devised to record distention of the bowel and the passage of fluid into the lumen. A detailed description of these studies is given.

Alvarez [164] also made studies on intestinal peristalsis in rabbits to determine the effects of nicotine. The drug tended to cut down intestinal peristalsis, and there seemed to be a gradient of susceptibility in the small bowel, the oral end being more susceptible. Most susceptible of all structures seemed to be certain synapses in Auerbach's plexus and the ganglion cells. The effects of the drug wore off quickly.

Roentgenologic studies on the gastrointestinal rate were performed by Wallace and his associates [165] on 52 ambulatory patients, none of whom had any disease that might affect gastrointestinal motility. The rate of progress of a barium sulfate meal was followed by observations at six hours and every twenty-four hours thereafter until evacuation was complete. Less than 10 per cent of the patients evacuated the barium in twenty-four hours, two thirds required three days and the remainder did not completely expel the barium meal until the fourth or the fifth day. This observation that the normal gastrointestinal tract may require as long as one hundred and twenty hours to expel a barium meal agrees with experimental results but represents a longer period than has formerly been obtained by a similar method of examination. Such a conception of normal gastrointestinal motility, of course, has been demonstrated by Alvarez, Hurst and others; but in view of the

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162. Robertson, E. C.: Intestinal Stasis Due to Low Mineral Intake, Am. J. Dis. Child. **53**:500 (Feb.) 1937.

163. Alvarez, W. C.: Peristaltic Rush Studied with New Apparatus, Am. J. Digest. Dis. & Nutrition **4**:225, 1937.

164. Alvarez, W. C.: Effect of Nicotine on Intestinal Peristalsis, Am. J. Digest. Dis. & Nutrition **4**:417, 1937.

165. Wallace, R. P.; Ehrenfeld, I.; Cowett, M.; Jolliffe, N.; Shapiro, B., and Sturtevant, M.: Motility of the Gastro-Intestinal Tract, Am. J. Roentgenol. **39**:64, 1938.

constant attempts of many pharmaceutic houses to push the sales of drugs to promote "proper evacuation," such evidence is refreshing and timely.

An excellent article on the action of morphine on the digestive tract is presented by Krueger.[166] In it he reviews the important experimental work since the original observations of Magnus (1908). The effects of the drug in causing gastric slowing and an increase in tone of the pyloric sphincter, augmented propulsion in the small intestine and digestive secretory changes, together with the mechanism of constipation secondary to the use of morphine, are all thoroughly covered in this article. The factors contributing to the constipating effect of the drug may include any or all of the following: decreased digestion due to diminution in biliary and pancreatic secretion, decreased propulsive activity, increased viscosity of the intestinal contents due to greater absorption of water and closure of the pyloric sphincter. Many of the points are hypothetic, but the article is intensely interesting.

Miller [167] has reviewed his important studies of the function of the small bowel by means of intubation experiments. He discusses in detail the factors involved in the maintenance of physiologic conditions in the small bowel. Under varying conditions the small intestine tends to maintain a reaction and an osmotic pressure similar to those of the blood plasma. The control of gastric evacuation is an important factor. The alkaline fluids of the duodenum are primarily involved in the neutralization of gastric acid. When the osmotic pressure of the acid chyme is high, reduction takes place partly by a process of dilution in the stomach and duodenum and partly by absorption in the duodenum. Miller attempts to correlate certain clinical observations on the basis of his experimental findings. For example, he believes that he can explain the fact that drinking water when the stomach is empty often leads to prompt evacuation of the bowel; the fact that the oral administration of hydrochloric acid in some cases of achlorhydria slows up gastric evacuation and controls gastrogenous diarrhea; the fact that in some instances a dilute solution of sodium bicarbonate taken when the stomach is empty gives a loose bowel movement, whereas a stronger solution may have no effect, and the fact that a small amount of highly concentrated sweet food may give a sense of distention because of the filling of the stomach with its own secretion in an attempt to dilute the hypertonic solution.

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166. Krueger, H.: Action of Morphine on Digestive Tract, Physiol. Rev. **17**:618, 1937.

167. Miller, T. G.: Intubation Studies of the Human Small Intestine: IX. Factors in the Maintenance of Physiologic Conditions, Rev. Gastroenterol. **4**:115, 1937.

Abbott, Karr and Miller [168] discuss the factors concerned in the absorption of dextrose from the jejunum and ileum, with particular reference to the ability of the small intestine to maintain isotonicity of its contents. The propulsive activity of the small intestine appears to increase as the concentration of dextrose rises above 5.4 per cent. Using a solution containing dextrose in the concentration naturally occurring in the jejunum and ileum (5 per cent and under), the authors found that the rate of absorption varied directly with the concentration.

Groen,[169] using a modification of the method of Miller and Abbott, studied the intestinal absorption of dextrose, galactose and levulose. He showed that a given length of the human small intestine during a constant interval absorbs a constant amount of simple sugar from a concentrated solution. The amount of sugar absorbed increases with an increase in intestinal surface and is proportional to the time allowed for absorption. The addition of dilute acid or alkali to the dextrose solution diminishes the amount of sugar absorbed. No influence of the immediately preceding diet or of starvation on the rate of absorption could be detected. A possible criticism of Groen's studies lies in the fact that he closed off only the lower part of the intestine and that therefore it was impossible for him to measure with absolute accuracy the area of absorbing surface involved in any given experiment.

Further studies by Groen [170] involved the absorption of dextrose from the small intestine in deficiency diseases. Using the same method as in the preceding experiments, he found a diminished absorption of dextrose in 3 patients with diarrhea associated with organic disease of the intestine and in 10 patients suffering from dietary deficiency, such as pernicious anemia and pellagra. In 2 cases of scurvy the absorption of dextrose appeared to be normal. Four of the patients with deficiency diseases were treated by means of an adequate diet, and after successful therapy normal absorption of dextrose was found. Groen feels that the diminished absorption in these cases was not due to increased motility but rather was the result of a defect in intestinal absorption.

Verzar,[171] in some interesting experiments on rats, apparently has shown that adrenalectomy is associated with definite changes in intestinal absorption. In adrenalectomized animals, dextrose seemed to be absorbed at the same rate as xylose; similar effects were noted on the

168. Abbott, W. O.; Karr, W. G., and Miller, T. G.: Intubation Studies of the Human Small Intestine: VII. Factors Concerned in Absorption of Glucose from Jejunum and Ileum, Am. J. Digest. Dis. & Nutrition **4**:742, 1938.

169. Groen, J.: The Absorption of Hexoses from the Upper Part of the Small Intestine in Man, J. Clin. Investigation **16**:245, 1937.

170. Groen, J.: The Absorption of Glucose from the Small Intestine in Deficiency Disease, New England J. Med. **218**:247, 1938.

171. Verzar, F.: Adrenal Cortex and Intestinal Absorption, Am. J. Digest. Dis. & Nutrition **4**:545, 1937.

absorption of fat. The administration of adrenal cortex extract restored the rate of absorption of dextrose to a level four times that of the absorption of xylose and increased the absorption of fat. Furthermore, the author believes that under the experimental conditions lactoflavine is not phosphorylated, a synthesis which probably takes place in the intestinal mucosa under normal conditions.

Sinclair and Smith [172] discuss the theory of phospholipid changes in the intestinal mucosa. This turnover of phospholipids within the mucous membrane lining the small intestine may be due to: (1) active combustion of phospholipid within the epithelial cells, (2) continued synthesis and carriage of phospholipid into the blood stream or (3) involvement of phospholipid as an intermediary product in the resynthesis of neutral fat. From the results of their studies the authors suggest that in the enzymic synthesis of phospholipid in the intestinal mucosa there is a selection of one molecule of saturated fatty acid for each molecule of unsaturated fatty acid.

The influence of fat on the absorption of dextrose from the alimentary canal was studied by Wishnofsky, Kane and Spitz [173] in a series of 11 diabetic patients. Their findings seem to indicate that, contrary to the usual opinion, the rate of absorption of dextrose mixed with fat is not appreciably less than that of dextrose alone.

Doubilet and Reiner [174] were able to study the absorption of fat from the ileum in a patient with a temporary Thiery fistula. They observed that the fluid secreted from the midportion of the ileum contained about 2 per cent lipoids. Olive oil and oleic acid were absorbed, even in the absence of bile acids, which in small amounts apparently had little or no effect on the rate of fat absorption. The administration of deoxycholic acid in large amounts increased the volume of fat excreted and subsequently tended to reduce the rate of its absorption.

Johnson [175] was able to separate and study colonic and ileal excretion in 3 patients with tumor of the cecum which necessitated both ileostomy and colostomy. In 2 of the 3 patients the content of the terminal portion of the ileum was acid at all times, and in the third patient it was usually acid. After an increase in peristaltic rate, however, the content became approximately neutral. As was to be expected, after the ingestion of a large amount of water the ileal content became more fluid,

172. Sinclair, R. G., and Smith, C.: Turnover of Phospholipids in Intestinal Mucosa, J. Biol. Chem. **121**:361, 1937.

173. Wishnofsky, M.; Kane, A. P., and Spitz, W. C.: Influence of Fat on Absorption of Dextrose from Human Alimentary Canal, Am. J. Digest. Dis. & Nutrition **4**:174, 1937.

174. Doubilet, H., and Reiner, M.: Absorption of Fat from the Ileum in Human Beings, Arch. Int. Med. **59**:857 (May) 1937.

175. Johnson, R. M.: Absorption and Excretion of Calcium and Phosphorus in Three Patients with Colostomy and Ileostomy, J. Clin. Investigation **16**:223, 1937.

with an associated increase in weight of the wet, dry and mineral excretion. Diuresis was associated with a concentration of the ileal excreta, and the more concentrated content contained more calcium and phosphorus per gram of dry weight than did the hydrated content. No evidence was obtained that viosterol had any specific effect on the absorption of calcium from the intestine in these cases. In the 3 patients the colon failed to excrete significant amounts of calcium and phosphorous at any time.

The absorption of iron from the intestine was found by Heath and his collaborators [176] to be inhibited when it was administered in small doses with relatively large amounts of mucin to patients with hypochromic anemia. These authors infer that increased amounts of mucus in the gastric contents in the presence of achlorhydria may play some role in the malabsorption of iron, especially when the diet is deficient in this substance.

Immediate and late effects of total colectomy or colonic exclusion with ileostomy were studied in 45 cases by Whittaker and Bargen.[177] It was found that the values for calcium in the serum were reduced after operation but returned to normal within one month. There were no other apparent disturbances in the equilibrium of the chemical constituents of the blood. As has been previously noted, definite dilatation of the terminal portion of the ileum was the usual result. The authors observed that the initial watery ileal discharge gradually thickened during the first three months, and they felt that this concentration of the ileal discharge was unrelated to the time necessary for ingested food to be expelled through the ileac stoma. They concluded that there was no fundamental change in motor activity or in intestinal response to ingested food throughout the prolonged period following operation and believe that no permanent metabolic deficiency followed ileostomy. They fail to emphasize, however, the immediate depletion that is so frequently seen in an aggravated form during the first weeks of the postopérative period following ileostomy. This depletion may be associated with various manifestations of deficiency disease and has been noted by numerous writers.

Welch, Masson and Wakefield [178] indicate one of the factors that may be operative in bringing about depletion during the postoperative

176. Heath, C. M.; Minot, G. R.; Pohle, F. S., and Alstead, G.: Influence of Mucin upon Absorption of Iron in Hypochromic Anemia, Am. J. M. Sc. **195**:281, 1938.

177. Whittaker, L. D., and Bargen, J. A.: Observations on Human Being Following Colectomy or Colonic Exclusion with Ileostomy, Surg., Gynec. & Obst. **64**:849, 1937.

178. Welch, C. S.; Masson, J. C., and Wakefield, E. G.: Clinical and Laboratory Findings After Excessive Loss of Intestinal Fluid from the Ileum, Surg., Gynec. & Obst. **64**:617, 1937.

period. These authors noted that there was an excessive loss of salt and water through the ileac stoma after ileostomy. Normally about 2 per cent of the total output of sodium is eliminated by the gastrointestinal tract and the remainder through the urinary tract. In their patient 91 per cent of the sodium in the diet was eliminated by the ileostomy, 9 per cent being recovered in the urine. Twenty-seven per cent of the estimated intake of chloride was eliminated by the ileostomy, although under ordinary conditions about 2 per cent is lost by way of the intestinal tract.

Intestinal obstruction is still a fertile field for investigation, both from the theoretic and from the practical point of view. Aird,[179] from a series of experiments on intestinal obstruction, concludes that the diminution in the volume of effective circulating blood from the loss of blood and plasma through the intestinal wall is a trivial factor in simple low intestinal occlusion and is not severe enough to cause death in cases of obstruction due to a closed loop. He thinks that it is an important feature of venous strangulation of the bowel and states that in a case of strangulation of a long loop, more than one third of the blood volume may be lost into the dilated intestinal vessels, tissue spaces of the intestinal wall and lumen, and into the peritoneal cavity. Extensive volvulus and extensive mesenteric vascular occlusion are thus primarily dangerous as forms of internal hemorrhage and are the only types of obstruction in which benefit is likely to result from blood transfusion. In cases of strangulation of an intestinal loop of medium length, Aird and Henderson[180] found a high concentration of histamine in the peritoneal transudate. This concentration was not high enough to be regarded as the sole lethal factor in fatal cases. It is thought that the specific toxins present in the transudate and responsible for death are still unknown.

Scudder, Zwemer and Truszkowski[181] produced intestinal obstruction in cats at various levels and noted a rise in the potassium content of the blood to levels which have previously been shown to be lethal. They suggest that potassium is the dialyzable toxic factor sought for in intestinal obstruction. Their findings are corroborated by those of Cutler and Pijoan,[182] who found that in high intestinal obstruction

179. Aird, I.: Experiments in Intestinal Obstruction: Role Played by Diminution of Effective Circulating Blood Volume in Acute Intestinal Obstruction, Edinburgh M. J. **44**:28, 1937.

180. Aird, I., and Henderson, W. K.: Intestinal Strangulation: Histamine Content of Peritoneal Transudate from Strangulated Intestinal Loops, Brit. J. Surg. **24**:773, 1937.

181. Scudder, J.; Zwemer, R. L., and Truszkowski, R.: Potassium in Acute Intestinal Obstruction, Surgery **1**:74 and 486, 1937.

182. Cutler, E. C., and Pijoan, M.: Certain Chemical Factors in Experimental High Intestinal Obstruction, Surg., Gynec. & Obst. **64**:892, 1937.

there is a definite factor of delayed absorption in the duodenum, with an associated increase in the potassium content of the blood. They, too, speculate as to the possible contributory role of a high potassium content as the cause of death in intestinal obstruction.

The concentration of volatile bases in the fluid contents of the intestine after low ileal obstruction in dogs was found by Hibbard and Kremen [183] to vary from 0.14 to 1.6 per cent. The volatile bases contained ammonia (50 per cent) and primary and tertiary amines. The length of life in cases of ileocecal obstruction was shortened when the animals were fed a meat diet rather than a meatless diet. When the p_H of the intestinal contents obtained from dogs dying of intestinal obstruction was raised to the antemortem level and placed in the intestinal loops of normal animals, toxic symptoms appeared and were followed by death. The distillate containing volatile bases was found to possess the same characteristics, but the base-free residue was entirely innocuous. The authors conclude that if volatile bases are present in sufficient concentration at an optimal p_H and if they are absorbed in cases of intestinal obstruction, severe toxic symptoms occur, with a fatal outcome.

An interesting clinical observation has been made by Estes,[184] who examined the obstructed loop in 4 cases after anastomosis for intestinal obstruction due to adhesions. In these cases diarrhea, pain, increased peristalsis and at times vomiting followed the first operation and led to resection of the sidetracked loop. Examination of the resected material revealed apparent stasis, some persistence of obstruction or constriction of the intestine, enteritis and ulceration. These findings were reproduced experimentally in dogs when anastomosis was made around an obstruction.

In an excellent review of his previous observations, Wangensteen [185] summarizes the hazards of intestinal obstruction and outlines in detail the rationale of treatment in this condition. Fine [186] also reviews his previous work and gives his further experience in the use of 95 per cent oxygen in deflating the distended bowel when other known nonoperative measures fail. Fine feels that the method is valuable in the treatment of distention, either of functional or of mechanical origin, and that it may be used to advantage before or after enterostomy for obstruction.

183. Hibbard, J. S., and Kremen, A. J.: Effect of the Volatile Base in Fluid Intestinal Contents on Dogs with Low Intestinal Obstruction, Surgery **3**:325, 1938.

184. Estes, W. L., Jr.: Enteritis of Obstructed Loop Following Entero-Anastomosis for Intestinal Obstruction, Ann. Surg. **105**:871, 1937.

185. Wangensteen, O. H.: Rationalizing Treatment in Acute Intestinal Obstructions, Surg., Gynec. & Obst. **64**:273, 1937.

186. Fine, J.; Hermanson, L., and Frehling, S.: Further Clinical Experiences with Ninety-Five per Cent Oxygen for the Absorption of Air from the Body Tissues, Ann. Surg. **107**:1, 1938.

Symptoms of oxygen poisoning were avoided by interrupting the administration of the gas every four to eight hours. The length of time necessary to produce a therapeutic effect varied with the individual case, in accordance with the volume of air to be absorbed and the relative extent of the surface available for absorption.

Various clinical aspects of disease of the small bowel are reported but for the most part do not warrant inclusion in this review. Freilich and Coe [187] discuss the clinical picture of jejunal intussusception, which is most commonly seen in adults and which is usually caused by a tumor due to some local cause of obstruction. In children, jejunal intussusception is commonly found with no apparent cause. In 3,784 cases of intussusception, an enteric type occurred in 14 per cent and a jejunal type in only 0.9 per cent of the cases.

Foucar [188] adds a rather complete review of the literature on syphilis of the gastrointestinal tract; in it he includes a description of 12 cases of syphilis of the small intestine and 1 interesting case of gumma of the transverse colon.

Among the many reports on regional ileitis, an article by Jellen [189] may be mentioned, mainly because it contains a good summary of the roentgenologic findings in this ill defined condition.

A good discussion of malignant tumor of the small intestine is presented by Nickerson and Williams.[190] The article includes a brief summary of the literature and a presentation of 10 cases in which the tumor was discovered at autopsy over a forty-year period. A corollary is found in an article by Rowe and Neely,[191] who discuss malignant growths of the small intestine and review in particular the roentgenologic aspects of the diagnosis of this condition.

An interesting clinical observation on spasmodic intestinal complications in pernicious anemia is presented by Weil and Ménètrier.[192] These authors describe the appearance of a pseudotumor, which produces clinical symptoms of pyloric constriction and gives the roentgenographic appearance of amputation of the pylorus. They believe that these mani-

187. Freilich, E. B., and Coe, G. C.: Jejunal Intussusception, Ann. Surg. **105**:183, 1937.

188. Foucar, F. H.: Syphilis of Gastro-Intestinal Tract: Report of Case of Gumma of Transverse Colon with Review of Literature, Am. J. Path. **13**:65, 1937.

189. Jellen, J.: Regional Ileitis: Review of Fifty Cases, Am. J. Roentgenol. **37**:190, 1937.

190. Nickerson, D. A., and Williams, R. H.: Malignant Tumors of the Small Intestine, Am. J. Path. **13**:53, 1937.

191. Rowe, E. W., and Neely, J. M.: Primary Malignancy of Small Intestine, Radiology **28**:325, 1937.

192. Weil, P., and Ménètrier, H.: Complications intestinales spasmodique au cours de l'anémie pernicieuse, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:145, 1937.

festations are due to muscular spasm and note that they disappear with liver therapy.

Experimental studies have been carried out by Chandler [193] on the nature of immunity to intestinal helminths, the work being done on white rats. The article is chiefly concerned with a discussion of the details involved in parenteral and intestinal immunity. The latter may be a part of the general immunity stimulated by parenteral immunization, although it may be developed independently.

Differences of opinion still exist as to the pathogenesis of infestations with Lamblia. Irazabal-Luigui,[194] in the belief that these parasites may be the cause of symptoms, sought for an effective specific agent. Tincture of carobine, pyrethrin, gentian violet, acetarsone, naphthalene and essence of turpentine were all used as therapeutic agents. The author concludes that essence of turpentine is of definite value in treating lambliasis, although it is not a specific. The other medications showed no beneficial effects.

THE COLON

In addition to numerous clinical and statistical studies of diseases of the colon, too numerous to be discussed in this review, a number of original contributions have appeared. These may be divided into three main groups: (1) contributions to the physiology of the colon, (2) descriptions of unusual diseases or complications and (3) contributions to the therapy of colonic diseases.

The contributions to the physiology of the colon include those dealing with metabolism, motility, dynamic pathologic anatomy, innervation, pharmacology, allergy and bacteriology. These subjects will be discussed in order.

An outstanding contribution to the knowledge of metabolic changes dependent on ulcerative colitis is made by Welch, Adams and Wakefield.[195] They studied 3 cases of idiopathic ulcerative colitis. The patients were given standard diets. The most outstanding metabolic feature was the abnormally high output of nitrogen in the feces. This was accompanied by a low urea nitrogen content of the blood, which varied from 8 to 20 mg. per hundred cubic centimeters. However, the excretion of fat in the feces was not in excess of that found for normal persons ingesting similar diets. The authors conclude that the increased fecal output of nitrogen was due to destruction of tissue and to the

193. Chandler, A. C.: Studies on Nature of Immunity to Intestinal Helminths: VI. General Résumé and Discussion, Am. J. Hyg. **26**:309, 1937.

194. Irazabal-Luigui, M.: Etudes expérimentales sur le traitement de la lambliase, Ann. de parasitol. **15**:29, 1937.

195. Welch, C. S.; Adams, M., and Wakefield, E. G.: Metabolic Studies of Ulcerative Colitis, J. Clin. Investigation **16**:161, 1937.

presence of such substances as blood and pus in the feces. They feel that the role of the rapid intestinal rate in preventing the absorption of fat has been greatly overemphasized.

Several studies of the motility of the colon have appeared. Galapeaux, Templeton and Borkon [196] placed tandem balloons in the colon of each of 4 cecostomized dogs and then introduced intraluminally quantities of gallbladder bile equal to the maximal amount of water which could be given without altering the motility of the colon. Usually this was about 20 cc. They found that the introduction of gallbladder bile consistently produced a reduction in the motility of the colon but resulted in defecation. The same quantity of water had no effect. The authors conclude that defecation may normally be accompanied by relaxation of the smooth musculature of the colon rather than by stimulation of it. Borkon and Templeton,[197] however, demonstrated in similar preparations that an enema of 100 to 200 cc. of oil retained within the rectum for two hundred minutes was accompanied by increased activity of the musculature in all parts of the colon. Lawson and Templeton [198] had previously shown that increasing the balloon pressure or introducing irritants above the inner sphincter of the anus inhibited the tone and activity in the proximal portion of the colon while stimulating active contractions in the rectal region. White and Jones [199] observed the number of peristaltic contractions in the human rectum through the sigmoidoscope. They found that although the resting rectum showed few or none, there were usually definite contractions after the application within the ampulla of the rectum of an irritant such as hypertonic salt solution or oil of turpentine. The application of the same irritant above the rectosigmoid junction, however, produced little or no peristaltic activity. All these findings are consistent with the hypothesis that the muscular activity incident to defecation is stimulated by the passage of fecal matter, possibly through relaxed circular musculature, into the ampulla of the rectum, where its presence through distention and local irritation produces activity of the musculature of the entire colon.

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196. Galapeaux, E. A.; Templeton, R. D., and Borkon, E. L.: The Influence of Bile on the Motility of the Dog's Colon, Am. J. Physiol. **121**:130, 1938.

197. Borkon, E. L., and Templeton, R. D.: The Influence of Oil Enemas on Colon Motility in the Dog, Am. J. Physiol. **118**:775, 1937.

198. Lawson, H., and Templeton, R. D.: Studies in the Motor Activity of the Large Intestine: I. Normal Motility in the Dog, Recorded by the Tandem Balloon Method, Am. J. Physiol. **96**:667, 1931; II. The Influence of Balloon Technique upon Colon Motility, ibid. **99**:87, 1931.

199. White, B. V., Jr., and Jones, C. M.: The Effect of Irritants and of Drugs Affecting the Autonomic Nervous System upon the Mucosa of the Normal Rectum and Rectosigmoid, with Especial Reference to "Mucous Colitis," New England J. Med. **218**:791, 1938.

Conflicting data on the presence of the gastrocolic reflex in the dog have appeared. Galapeaux and Templeton [200] found that filling the stomach with a mixture of yeast and buttermilk or even inflating it with a balloon resulted in stimulation of colonic activity in the dog. Slive and Fogelson,[201] however, using balloons introduced through fistulas in different parts of the colon, were unable to demonstrate the gastrocolic reflex, although they did demonstrate an appetite or feeding reflex. A feeding reflex would hardly account for colonic motility after the inflation of a balloon in the stomach, as reported by the former workers.

Barclay and Franklin [202] investigated the physiology of the defecation reflex. They discovered that if digital compression of the bladder or of the large intestine was performed, particularly if there was passage of feces into the rectum, there resulted a marked reflex contraction of the diaphragm and abdominal muscles. These observations suggest that the act of defecation is a purely involuntary affair after the proper stimulus to its initiation has occurred.

Hartmann [203] advances the idea that the pathologic anatomy of diverticulosis is dependent on the presence of localized areas of muscular weakness and of spasm. He reports an instance in which a surgeon who was operating on an inflamed rectosigmoid junction witnessed a powerful contraction of the intestine, during which the taeniae separated and a row of little diverticula popped out. Hence, Hartmann believes that diverticula of the colon are usually pulsion diverticula and that the concept of a state of latent diverticulosis may well be tenable. He attributes much importance to the possible role of so-called mucous colitis and of lead colic in conditioning this state.

The autonomic innervation and the pharmacology of the colon are best considered together. The contributions which deal with the neurologic aspects of colonic physiology are those of Lawson and Holt [204] and of Manning, Hall and Banting.[205] Lawson and Holt studied the effect of surgical decentralization and subsequent removal of the inferior

200. Galapeaux, E. A., and Templeton, R. D.: The Influence of Filling the Stomach on Colon Motility, Am. J. M. Sc. **195**:230, 1938.

201. Slive, A., and Fogelson, S. J.: Colon Motility: An Experimental Study of the Colon in the Dog, Am. J. Digest. Dis. & Nutrition **4**:17, 1937.

202. Barclay, A. E., and Franklin, K. J.: Reflexes from Bladder and Large Intestine, J. Physiol. **90**:478, 1937.

203. Hartmann, J.: Zur funktionellen Pathologie der Divertikulosis des Kolons, München. med. Wchnschr. **84**:252, 1937.

204. Lawson, H., and Holt, J. P.: The Control of the Large Intestine by the Decentralized Inferior Mesenteric Ganglion, Am. J. Physiol. **118**:780, 1937.

205. Manning, G. W.; Hall, G. E., and Banting, F. G.: Vagus Stimulation and the Production of Myocardial Damage, Canad. M. A. J. **37**:314, 1937.

mesenteric ganglion in dogs. Observations on the motility of the colon were made by the balloon method. They found that division of the spinal rami of the inferior mesenteric ganglion resulted in a decreased tone in the anal canal and an increased tone in the middle portion of the colon but was without effect on the height or the rate of intestinal conditions. Subsequent removal of the inferior mesenteric ganglion had no constant effect on muscle tone but greatly increased the height of contractions. Manning, Hall and Banting studied the effect of direct stimulation of the vagus nerve on the myocardium and on the gastrointestinal tract. Hall, Ettinger and Banting [206] had previously produced myocardial damage and ulceration in the stomach and duodenum by daily intravenous administration of acetylcholine. In anesthetized animals they failed to obtain these changes by direct vagal stimulation. Manning, Hall and Banting, however, developed a technic for chronically stimulating the vagus nerve of unanesthetized animals and produced lesions similar to those resulting from the intravenous use of acetylcholine. White and Jones,[199] by direct observation through the sigmoidoscope, noted changes, consisting of diffuse injection, secretion of mucus, dilatation of veins and a mild degree of spasm of the rectosigmoid junction after the oral ingestion of acetylbetamethylcholine chloride and after the topical application of physostigmine sulfate and pilocarpine hydrochloride. They did not furnish evidence as to the effect of direct stimulation of the parasympathetic nervous system on these tissues. Starr [207] studied the pharmacologic effects of carbaminoylcholine chloride in normal persons and in persons with peripheral vascular disease. He concluded that its cholinergic action on the gastrointestinal tract, as compared with that on the circulatory system, was far greater than that of acetylbetamethylcholine chloride. Bosse [208] used the drug therapeutically in 62 cases of postoperative intestinal distention and atony of the bladder. It relieved urinary retention in 75 per cent of the 41 cases in which it was tried and was found effective in 21 cases of postoperative distention. The author feels that carbaminoyl choline chloride was considerably more effective than prostigmine and safer than the pituitary preparations. Myerson, Schube and Ritvo [209] observed the

206. Hall, G. E.; Ettinger, G. H., and Banting, F. G.: An Experimental Production of Coronary Thrombosis and Myocardial Failure, Canad. M. A. J. **34**:9, 1936.

207. Starr, I.: Carbaminoylcholine (Doryl or Lentin): Its Action on Normal Persons, in Peripheral Vascular Disease, and in Certain Other Clinical Conditions, Am. J. M. Sc. **193**:393, 1937.

208. Bosse, U: Doryl zur Behandlung der Darm- und Blasenatonie, Klin. Wchnschr. **16**:1356, 1937.

209. Myerson, A.; Schube, P. G., and Ritvo, M.: Effect of Acetyl-Beta-Methyl-Choline on the Atonic Colon, Radiology **28**:552, 1937.

effect of acetylbetamethylcholine chloride on the atonic colon in certain cases of schizophrenia. They found that a 30 mg. dose administered subcutaneously generally produced increased tonus and motility of twenty-four hours' duration. Two papers on drugs which supposedly inhibit the muscular activity of the colon are also of interest. Quigley [210] demonstrated that methylhomatropine bromide was less effective than atropine sulfate in its effect on gastrointestinal motility. In the unanesthetized dog, doses one and one-half times the necessary dose of atropine sulfate were required to inhibit completely the motility of the stomach. It required doses six times as large as the necessary dose of atropine sulfate to inhibit completely the activity of the colon. Novatropin is alleged to be six tenths as toxic as atropine sulfate. Boyd [211] reports investigations on the properties of benzedrine sulfate which indicated that it possesses a specific direct effect, causing contraction of intestinal and uterine smooth muscle. This activity was also shared by ephedrine hydrochloride but not by epinephrine hydrochloride. Hence any relaxing effect which benzedrine may have through its effect in inhibiting the end organs of the sympathetic nervous system is at least in part offset by a direct antagonistic action on smooth muscle.

A common denominator of innervation of the autonomic nervous system, chemical mediation of nerve impulses, capillary physiology, allergy and, more specifically, wheal formation is histamine. Felix,[212] inspired by the work of Mellanby and of Koessler and Hanke, who have shown that histamine introduced into the gastrointestinal tract rapidly disappears, studied the effect of a preparation of dried intestinal mucus ("torantil") on histamine. If injected simultaneously with histamine, torantil was found to be without effect in modifying the action of the histamine. If incubated with histamine at 37 C. for twenty-four hours, however, it completely inhibited the action of the latter. The extract of mucus was rendered completely inert by heating to 70 C. for thirty minutes and was inert at a p_H of from 2.5 to 5. Because of its latent period, thermolability and optimum p_H, the author concludes that torantil possesses the qualities characteristic of a true enzyme. Attempts to treat intestinal disorders with this preparation will be discussed in the last paragraphs of the present review.

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210. Quigley, J. P.: The Relative Effectiveness of Atropine and Novatropin on Gastric and Colonic Motility of the Unanesthetized Dog, J. Pharmacol. & Exper. Therap. **61**:30, 1937.

211. Boyd, E. M.: The Effect of Benzedrine Sulphate on the Bowel and Uterus, Am. J. M. Sc. **195**:445, 1938.

212. Felix, J.: Experimental and Clinical Investigations of the Action of Histaminase Contained in Extracts of the Mucous Membrane of the Intestines on Histamine, Acta med. Scandinav. **95**:1, 1938.

In the field of allergy, Gray and Waltzer [213] inoculated into the mucosal wall of the rectum serum from a patient known to be sensitive to peanut oil. When peanut meal was subsequently fed by mouth the sites of passive transfer into which the oil had been inoculated could be seen to swell up and become edematous, gradually to become deep red, to become covered with mucus and finally, in the course of an hour or so, to fade away. The changes commenced six to thirty minutes after the ingestion of the peanut oil. The authors concluded that the changes were due to hematogenous transmission of the antigen. From their description the changes must have resembled closely those observed by White and Jones after the topical application of cholinergic drugs.

Contributions to the bacteriology of several diseases of the colon have appeared. Goodpasture [214] studied a patient with typhoid at autopsy, one and one-half hours after death. He observed within the plasma cells small gram-negative bacilli, which he assumed to be Escherichia typhi. They were present in intestinal lesions and also in regional lymph nodes. He advances the hypothesis that the young plasma cell is an essential cellular host in the typical disease in human beings and serves as a protecting and nourishing medium through the period of incubation and throughout the active course of the disease.

Castellani [215] describes a rare and little known form of chronic colitis, which he termed *métadysenterie chronique*. He says that the disease is due to a group of organisms for which Cerruti coined the generic name Castellanus. Like true dysentery organisms, these organisms do not produce gas on any sugar, but they ferment lactose, with the formation of acid, and slowly coagulate milk. Some strains are motile and others nonmotile. One of the strains is considered to be identical with Sonne's bacillus. The disease is widely distributed in the tropics and subtropics and all over Europe and is characterized by recurrent attacks of simple diarrhea, often interspersed with long remissions. There is no pus or blood in the feces, and the clinical picture often closely resembles that of mucous colitis. A detailed classification of the various strains of organisms, with their characteristic fermentation reactions, is given. Mones and Sanjuan [216] report on the etiology of ulcera-

213. Gray, I., and Waltzer, M.: Studies in Mucous Membrane Sensitivity: III. The Allergic Reaction of the Passively Sensitized Rectal Mucous Membrane, Am. J. Digest. Dis. & Nutrition **5**:707, 1938.

214. Goodpasture, E. W.: Concerning the Pathogenesis of Typhoid Fever, Am. J. Path. **13**:175, 1937.

215. Castellani, A.: Un type peu connu de colite chronique, Presse méd. **45**: 1823, 1937.

216. Mones, F. G., and Sanjuan, P. D.: Colitis ulcerosas graves no amibianas etiologia, diagnostica y tratamiento medico, abstracted by J. A. Bargen and A. E. Mendes Ferreira, Am. J. Digest. Dis. & Nutrition **4**:247, 1937.

tive colitis, advancing the thesis, supported by some evidence, that the disease is caused by a filtrable virus. They were able to find the gram-positive diplostreptococcus of Bargen with about equal frequency in a series of 25 cases of idiopathic ulcerative colitis and in a control group of similar size. They were relatively unsuccessful in producing experimental lesions with this organism. They prepared a filtrable virus from ulcers of patients with ulcerative colitis and succeeded in producing ulcerative lesions of the gastrointestinal tract in animals after the intravenous injection of this virus. They found that the virus lost virulence if cultivated on solid medium but retained it if grown on Rosenow's medium. They feel that the virus grew anaerobically at the expense of living streptococci. Fifty-five per cent of all the rabbits which were given injections became ill, while 88 per cent of the rabbits which were given injections of the virus grown on Rosenow's medium became ill. In almost all of them diarrhea developed, sometimes with bloody stools. The digestive tracts showed lesions varying from congestion to deep ulceration. The experimental disease in dogs was more like the disease in human beings than like that in rabbits. More than 80 per cent of the dogs that were given injections became ill. The authors offer no specific therapeutic suggestions.

Paulson and Andrews [217] report, after an extensive study of the value of complement fixation tests for amebic infestation, that positive results were obtained for 66.7 per cent of the patients with known amebiasis. A number of positive results were also reported for persons with no clinical or other laboratory evidence of infestation. The tests were made on 150 persons, and the samples of blood were sent to three different laboratories in Baltimore. Craig, Sherwood and Arnold antigens were used. Some of the serums were tested with more than one of the antigens, and the incidence of positive reactions varied considerably. The gross number of positive reactions for persons with known amebiasis (66.7 per cent) was lower than the figures published by the aforementioned authors or by Tsuchiya. Paulson and Andrews conclude that the test as performed routinely in the clinical laboratory can be considered as a diagnostic aid but that primary importance should not be attached to it.

Bauknecht,[218] in studying the effect of indol and its derivatives on the inhibition of the growth of bacteria, found that indol, skatol, indol acetate and indol propionate had an effect in inhibiting the growth of

217. Paulson, M., and Andrews, J.: A Comparative Evaluation in Clinical Practice: Complement Fixation in Amebiasis, Arch. Int. Med. **61**:562 (April) 1938.

218. Bauknecht, H.: Die entwicklungshemmende Wirkung von Indol auf Bakterien, Zentralbl. f. Bakt. **140**:101, 1937.

bacteria far in excess of that of phenol. The concentrations of indol and of phenol required to inhibit the growth of various organisms were as follows:

Organism	Indole	Phenol
Lactic acid bacilli	1:2,000	1:250
Bacillus coli	1:2,000	1:500
Bacillus proteus	1:2,000	1:250
Streptococcus haemolyticus	1:2,000	1:500
Staphylococcus aureus	1:4,000	1:250

In view of such findings one is led to speculate whether the deleterious effects that are usually ascribed to indol and its derivatives may not be counterbalanced by beneficial inhibitory effects on bacterial growth in the bowel.

The descriptions of unusual diseases or of unusual complications of diseases of the colon include a large number of subjects, which in many instances are only superficially related to one another. Perhaps the most important of these is the widening recognition of the intestinal manifestations of lymphogranuloma venereum. Chapman and Hayden [219] report on a series of 30 patients with "lymphogranuloma inguinale" from various parts of New England. Of these 30 patients, 10 showed only local adenitis and genitourinary manifestations, 4 showed chronic gastrointestinal disease without anal stricture and 16 showed anal strictures with or without other manifestations of the disease. Of the 4 showing gastrointestinal disease without anal stricture, 3 had localized proctitis, while the fourth had regional ileitis. The entire series of 30 patients showed a positive reaction to the Frei test. Paulson [220] separated from the general group of patients with idiopathic ulcerative colitis a small number who gave a positive reaction to the Frei test in whom an antigen prepared from the intestinal content was capable of evoking a positive cutaneous reaction. The positive reaction could be produced either in the person from whom the antigen was isolated or in some other person with venereal lymphogranuloma. Paulson feels that he has presented evidence that the syndrome of ulcerative colitis in certain instances can well be a manifestation of venereal lymphogranuloma. Spiesman, Levy and Brotman,[221] in a study of 138 patients with

219. Chapman, E. M., and Hayden, E. P.: Lymphogranuloma Inguinale, New England J. Med. **217**:45, 1938.

220. Paulson, M.: A New Diagnostic Intradermal Reaction with Bowel Antigen Indicating the Presence of the Virus of Venereal Lymphogranuloma in the Intestine and Differentiating the Colitis Associated with That Virus, J. A. M. A. **109**:1880 (Dec. 4) 1937.

221. Spiesman, M. G.; Levy, R. C., and Brotman, D. M.: Lymphogranuloma Inguinale: Rectal Stricture and Prestricture, Am. J. Digest. Dis. & Nutrition **3**:931, 1937.

rectal stricture in the Cook County Hospital, Chicago, found that 115 gave a positive reaction to the Frei test and that 89 per cent were women with reputedly low moral standards. Haim and Mathewson [222] found 23 cases of venereal lymphogranuloma in 51 cases of benign rectal stricture in San Francisco. They found a high incidence of positive reactions to the Frei test among patients in a marine hospital and a much lower incidence among the patients in the wards of a general hospital.

The presence of colitis localized on the right side of the colon also received a moderate amount of attention. Crohn and Berg [223] found that about 10 per cent of their patients with idiopathic ulcerative colitis had lesions localized in the right or transverse colon or both but showed little evidence of disease in the rectum or sigmoid flexure. Dudley and Miscall [224] also emphasize the fact that tumors much like those of regional ileitis can be found in various parts of the gastrointestinal tract, including the colon; and Illtyd-James [225] reports a case in which the picture was similar to that in regional ileitis but the lesions were located wholly within the colon. Ralphs [226] reports 3 cases of chronic inflammatory tumor of the gastrointestinal tract: in 2 cases in the ileocecal and in 1 case in the pelvirectal region. There is still much confusion in the use of such terms as colitis, regional ileocolitis and inflammatory tumor, and it is not clear from some of the papers whether the tumor was necessarily idiopathic. There is apparently a field where regional ileitis and ulcerative colitis mimic one another, and a sharp demarcation is still further obscured by such diagnostic possibilities as tuberculosis, diverticulitis, syphilis, venereal lymphogranuloma and neoplasm.

A rare form of granuloma which may be mentioned is amebic stenosis. Christopher [227] reports on a case of amebic dysentery in which the inflammatory process progressed to the point where resection of the entire right and the transverse colon was necessary to relieve intestinal obstruction. Christopher found in the literature a report of only 1 previous case of amebic granuloma in which surgical treatment was required, a fatal case reported by Youmans.

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222. Haim, A., and Mathewson, C., Jr.: The Incidence of Lymphogranuloma Inguinale in San Francisco, J. A. M. A. **108**:961 (March 20) 1937.

223. Crohn, B. B., and Berg, A. A.: Right-Sided (Regional) Colitis, J. A. M. A. **110**:32 (Jan. 1) 1938.

224. Dudley, G., and Miscall, L.: Inflammatory Tumors of the Gastrointestinal Tract, Ann. Surg. **107**:55, 1938.

225. Illtyd-James, T. G.: Chronic Regional Colitis, Brit. J. Surg. **25**:511, 1938.

226. Ralphs, F. G.: On Chronic Inflammatory Tumors of the Gastrointestinal Tract, Brit. J. Surg. **25**:524, 1938.

227. Christopher, F.: Stenosis of the Large Bowel Due to Amebiasis, Surgery **3**:75, 1938.

A number of congenital anomalies, principally of the right colon, are reported by various workers but hardly warrant comment.

Shanks [228] has made a study of the position and relations of the colon relative to the development of anomalies. He feels that anomalies may be due to alterations in length, rotation, fixation or size and attempts to explain most of the common variations on this basis. Hardly to be explained on this basis were 3 cases of solitary diverticulum of the cecum reported by Bennett-Jones,[229] who in addition to his own series cites 17 cases previously reported in the literature. In many cases the diverticulum became the site of inflammation and produced symptoms much like those encountered in appendicitis. However, only 1 of the 11 cases reviewed in the literature terminated in perforation. Another rare congenital abnormality is microcolon, of which 2 cases are reported by Ewing and Cooke.[230] Both occurred in 3 day old children who died postoperatively. That congenital microcolon is a rare anomaly is attested by the fact that in a series of 111,451 consecutive autopsies reported from Vienna, congenital narrowing of the colon was encountered in only 2 cases, while in a series of 150,000 consecutive autopsies reported from Leningrad it was encountered in only 9 cases.

Several unusual causes of intestinal obstruction are also described. Eliason and Erb [231] were able to find in the literature only 38 cases of intestinal obstruction during pregnancy which were attributed to enlargement of the uterus. They add reports of 3 patients from the obstetric service of the Hospital of the University of Pennsylvania. They feel that relief can sometimes be obtained by changes in position and enemas but that otherwise laparotomy and cesarean section are indicated. Hepburn [232] and Cattell [233] each report instances of intestinal obstruction resulting from endometrial implants. Cattell divides the types of involvement of the bowel into three groups: (1) involvement of the rectovaginal septum, (2) involvement of the rectum and sigmoid flexure and (3) endometrial involvement of the entire intestinal wall. He cites 2 cases representing each type. In those cases in

228. Shanks, S. C.: Congenital Abnormalities of the Colon, Brit. J. Radiol. **4**:261, 1937.

229. Bennett-Jones, M. J.: Primary Solitary Diverticulitis of the Cecum, Brit. J. Surg. **25**:66, 1937.

230. Ewing, J. B., and Cooke, W. E.: Two Cases of Congenital Microcolon, Brit. J. Surg. **25**:506, 1938.

231. Eliason, E. L., and Erb, W. H.: Intestinal Obstruction Complicating Pregnancy, Surgery **1**:65, 1937.

232. Hepburn, J. J.: Endometriosis as a Cause of Acute Intestinal Obstruction, New England J. Med. **217**:6, 1937.

233. Cattell, R. B.: Endometriosis of the Colon and Rectum with Intestinal Obstruction, New England J. Med. **217**:9, 1937.

which the intestinal lesion was discrete, resection of the sigmoid flexure was performed; in the others the bowel was not resected. In all cases extensive pelvic treatment was carried out, and all the patients showed good recovery. Foucar [188] reports 1 case of gumma of the transverse colon. He has collected reports of only 4 cases from the literature, in none of which had a flexure been affected.

Uncommon tumors or combinations of tumors are also reported. Maingot [234] and Pemberton and Waugh [235] each cite instances of the simultaneous development of carcinoma of the stomach and carcinoma of the colon. Wyatt [236] discusses carcinoid or argentaffine tumors and concludes that they are, contrary to general opinion, potentially malignant. He cites 1 case in which there were metastases, but the patient did well after removal of the primary and secondary lesions. Miller and Sweet [237] emphasize the importance of inheritance in the development of multiple polyposis of the colon and also the frequency with which such lesions eventually become malignant.

Two unusual genitourinary complications were also noted. Hepler [238] describes 2 cases of nonobstructive congenital megaloureter, in 1 of which the condition was associated with megacolon. Feldman [239] describes the development of renocolic fistula as a complication of pyelonephritis. In his patient the renal pelvis had perforated through into the large bowel, and the resultant lesion was mistaken for carcinoma of the colon when an enema of barium sulfate was given.

Wilkie,[240] in the course of twenty years of practice, has seen 4 patients with benign ulcer of the ascending colon. In these 4 cases the ulcer became manifest through utterly different clinical syndromes. In view of the extreme rarity of the condition they merit listing separately:

Case 1.—A 45 year old man complained of chronic constipation and pain in the right lower quadrant of the abdomen. At operation a mass was present in the ascending colon which looked much like carcinoma. Pathologic study of the

234. Maingot, R.: Primary Carcinoma of the Stomach, Sigmoid and Colon Occurring Simultaneously, Brit. M. J. **1**:118, 1938.

235. Pemberton, J. J., and Waugh, J. M.: Primary Carcinomas of the Stomach and Sigmoid Flexure Occurring Simultaneously in the Same Individual, Surgery **2**:211, 1937.

236. Wyatt, T. E.: Argentaffine Tumors of the Gastro-Intestinal Tract, Ann. Surg. **107**:260, 1938.

237. Miller, R. H., and Sweet, R. H.: Multiple Polyposis of the Colon, Ann. Surg. **105**:511, 1937.

238. Hepler, A. B.: Nonobstructive Dilatations of the Upper Urinary Tract in Children, J. A. M. A. **109**:1602 (Nov. 13) 1937.

239. Feldman, M.: Renocolic Fistula, Am. J. Digest. Dis. & Nutrition **4**:110, 1937.

240. Wilkie, D.: Simple Ulcer of the Ascending Colon and Its Complications, Surgery **1**:655, 1937.

resected lesion revealed a deep ulcer, much like a gastric ulcer, with induration and small cell infiltration but no evidence of cancer.

CASE 2.—A 64 year old woman complained of chronic constipation and pain in the right lower quadrant of the abdomen. Physical examination revealed a tender mass in that quadrant. Subsequently a nontender necrotic swelling developed in the inguinal region which looked like a hernia but contained gas. It was found to be continuous with an extraperitoneal cavity extending from the kidney to the pelvis. Autopsy showed an ulcer, 5 mm. in diameter, which had perforated through the posterior aspect of the ascending colon.

CASE 3.—A 56 year old woman complained of chronic constipation and of diarrhea of eight days' duration. Severe pain and tenderness then developed in the right lower quadrant of the abdomen. She died, and autopsy showed generalized peritonitis resultant on the anterior perforation of an ulcer in the ascending colon.

CASE 4.—A 49 year old woman complained of distention and of dragging pain in the right lower quadrant of the abdomen of ten years' duration. At operation a fibrosed stellate scar was present in the ascending colon. There was also a duodenal ulcer.

Two unusual conditions simulating acute abdominal conditions are also placed on record. Cullen and Brodel [241] describe a syndrome characterized by acute tenderness in the lower portion of the abdomen produced by hemorrhage into the sheath of the rectus abdominis muscle. The symptoms usually occurred after exertion or during pregnancy, and Cullen says that on physical examination it was determined that the tenderness was localized to the area of the muscle sheath. Robertson [242] emphasizes that in hyperthyroidism it is possible for a state of abdominal distress to develop which simulates an acute abdominal catastrophe. In 1 of the 3 cases cited the patient had been given thyroid by mouth. Severe pain developed in the right lower quadrant of the abdomen and was accompanied by diarrhea and a white blood corpuscle count of 27,000 per cubic millimeter. At operation, by a well known surgeon, a normal appendix was removed.

Ferguson [243] reports 2 cases of carcinoma of the pelvic viscera in which irradiation was followed by distressing rectal symptoms. Cramps, severe tenesmus, bloody diarrhea and, in 1 case, almost complete incon-

241. Cullen, T. S., and Brodel, M.: Lesions of the Rectus Abdominis Muscle Simulating an Acute Intraabdominal Condition: I. Anatomy of the Rectus Abdominis Muscle, Bull. Johns Hopkins Hosp. **61**:295, 1937. Cullen, T. S.: II. Hemorrhage Into or Beneath the Rectus Muscle Simulating an Acute Abdominal Condition, ibid. **61**:317, 1937.

242. Robertson, W. E.; Wohl, M. G., and Robertson, H. F.: Hyperthyroidism Masked by Symptoms of Acute Abdominal Catastrophe, J. A. M. A. **108**:623 (Feb. 20) 1937.

243. Ferguson, L. K.: Secondary Effects of Radiation upon the Rectum Following the Treatment of Extrarectal Pelvic Lesions, Am. J. Digest. Dis. & Nutrition **4**:712, 1938.

tinence occurred several months after the treatment. Examination revealed extreme tenderness of the rectum, stenosis due to contraction of the entire rectal wall and a pale, ulcerated mucosa. Treatment includes keeping the stools soft if stenosis is marked and colostomy if necessary. This reaction should be distinguished from extension or metastasis of a neoplasm, which it simulates.

The contributions to the therapy of diseases of the colon may best be divided into those which are primarily surgical and those which are primarily medical. Devine [244] describes a technic for operating on the isolated colon after the fecal stream has been diverted. By an ingenious method he performs an initial double-barrel proximal colostomy in which the two ostia are widely separated. In this way it is possible completely to protect the isolated colon from fecal contamination and by daily lavage to approach a state of sterility. Devine has found that it is possible to perform the most radical resection in the distal portion of the colon and rectum without the mortality generally associated with operative work in that region. Reestablishment of fecal flow through the colon is easily brought about through the use of an enterotome, which cuts through the walls of the colon directly beneath the double-barreled enterostomy.

Adson,[245] in discussing the surgical treatment of Hirschsprung's disease, outlines four operations on the sympathetic system in current use: (1) the Wade operation, consisting of removal of the first and second lumbar sympathetic ganglions on the left; (2) the Judd and Adson operation, consisting of bilateral removal of the second, third and fourth lumbar ganglions and the intervening trunk; (3) the Rankin and Learmouth operation, consisting of resection of the inferior mesenteric nerves and the presacral nerve, and (4) the new Adson operation, consisting of removal of both trunks, the second, third and fourth lumbar ganglions, the superior hypogastric plexus and the presacral nerve. After this last type of operation the only sympathetic fibers remaining intact are those which course down along the inferior mesenteric artery to the lower portion of the colon and anus. Adson reports follow-up studies of 22 patients with Hirschsprung's disease or an atonic colon, 3 having had extensive splanchnic resection and the rest a limited operation. The patients were from 5½ months to 19 years of age, most of them being under 6 years of age. Most of those in whom the disorder was on the left side were greatly helped; those with symptoms on the right side responded distinctly less well. Two patients

244. Devine, H.: Operation of a Defunctioned Distal Colon, Surgery **3**: 165, 1938.

245. Adson, A. W.: Hirschsprung's Disease: Indications for and Results Obtained by Sympathectomy, Surgery **1**:859, 1937.

died, 1 on the operating table and 1 a day later. Leriche [246] outlines the same group of procedures and, in general, agrees that after any one of them the intestinal movements usually become regular and remain regular with or without a laxative. He decided therefore to try a much simpler operation, i.e., unilateral resection of the splanchnic nerve. This he did in 4 cases (2 children and 2 adults), with excellent results.

Another semisurgical procedure is the use of the electrocautery for the treatment of carcinoma of the rectum. Thorlakson and Hay [247] in 10 cases of carcinoma of the rectum or rectosigmoid juncture, employed electrocoagulation; they feel that it offers a means of palliative treatment under certain indications: (1) advanced age, (2) marked general debility, (3) tumor of the rectal ampulla located posteriorly and laterally and (4) refusal of radical surgical treatment. They claim good palliative results in certain instances. However, it seems that there is danger of perforation through peritonealized areas of the rectum and of the rectosigmoid juncture, with the development of generalized peritonitis, and in most instances this hazard should contraindicate such a procedure.

Pneumoperitoneum in the treatment of intestinal tuberculosis is reviewed by Salkin.[248] He claims good results or complete cure in 72 per cent of 76 white patients and in 76 per cent of 17 Negroes; in other words, in 73 per cent of a total of 95 patients so treated. Unfortunately, he does not publish data regarding a control series treated in another manner; however, the figures appear to be strikingly good. He quotes Banyai and others who have previously obtained good results with the method.

Another form of physical treatment which is reported is the use of artificial fever in ulcerative colitis. Ferguson, Fetter and Schnabel [249] treated 4 patients with the Kettering hypertherm. In each instance they maintained a temperature of from 104 to 105 F. for two and one half hours three times a week. Each patient received from seven to twelve treatments. The authors feel that they obtained good clinical improvement by this method and that the proctoscopic picture showed a corresponding change toward the normal. It seems probable that such results, if obtained consistently, are similar in character to those claimed

246. Leriche, R.: De la section des splanchniques dans la mégacolon non compliqué avec or sans dolichocolon, Presse méd. **45**:1851, 1937.

247. Thorlakson, P. H. T., and Hay, A. W. S.: Carcinoma of the Rectum and Rectosigmoid, Canad. M. A. J. **38**:107, 1938.

248. Salkin, D.: Pneumoperitoneum in Intestinal Tuberculosis: An Appraisal of Various Therapeutic Procedures, Am. Rev. Tuber. **33**:435, 1936.

249. Ferguson, L. K.; Fetter, F., and Schnabel, T. G.: Artificial Fever in the Treatment of Ulcerative Colitis: A Preliminary Report, Am. J. Digest. Dis. & Nutrition **4**:487, 1937.

by the enthusiastic supporters of so-called specific serum therapy. Nor must it be forgotten that spontaneous remissions are characteristic of the disease.

The more purely medical forms of treatment vary considerably in their originality. At least four papers have appeared on the use of aluminum compounds. Eyerly and Breuhaus [250] advocate strongly the use of aluminum silicate (kaolin) and of aluminum hydroxide in ulcerative colitis, claiming that the action of these substances is twofold: (1) to remove bacteria mechanically and (2) to remove toxins by adsorption. These actions were originally demonstrated for kaolin by Braafledt, in 1923. Crohn, in 1929, showed that aluminum hydroxide could effectively be used as a substitute for other alkaline substances in the treatment of peptic ulcer. Smith [251] prepared a mixture of 20 per cent aluminum silicate and 2.5 per cent aluminum hydroxide suspended in water. Fecal suspensions were placed in graduated cylinders at 37 C. (1) alone, (2) with 3 Gm. of kaolin and (3) with 3 Gm. of the mixture of kaolin and aluminum hydroxide. Bacterial counts which were made at intervals revealed that the mixture of kaolin and aluminum hydroxide was about five times as effective as kaolin alone in adsorbing or in inhibiting the growth of bacteria. Fradkin [252] used approximately such a mixture as an enema for the relief of local symptoms in a case of ulcerative colitis. He employed an enema consisting of 20 per cent kaolin (aluminum silicate), 10 per cent liquid petrolatum and 70 per cent aluminum hydroxide gel and introduced 10 ounces (300 cc.) three times a week. He feels that the patient received definite relief. Emery,[253] however, advises against the wholesale use of adsorbants, because of the danger of adsorbing vitamins and because he thinks the adsorbants are likely to dry in the colon, a risk which he feels need not be considered in ulcerative colitis. He considers that neither kaolin nor barium sulfate should be used in cases of diverticulitis, because of the danger of perforating the diverticulum. Without adequate supporting data, the question arises as to whether such objections are not rather academic.

The use of apple powder in the treatment of acute diarrhea has received some attention. Manville [254] outlines rather extensively the

250. Eyerly, J. B., and Breuhaus, H. C.: Treatment of Ulcerative Colitis with Aluminum Hydroxide and Kaolin, J. A. M. A. **109**:191 (July 17) 1937.

251. Smith, W.: A Comparison Between the Adsorptive Action of Kaolin and Kaolin-Alumina Mixture on Fecal Bacteria, Lancet **1**:438, 1937.

252. Fradkin, W. Z.: Control of Rectal Bleeding in Convalescent Ulcerative Colitis Patient, J. Lab. & Clin. Med. **22**:877, 1937; abstracted J. A. M. A. **109**:464 (Aug. 7) 1937.

253. Emery, E. S., Jr.: The Pharmacopeia and the Physician, Use of Absorbents in Gastro-Intestinal Diseases, J. A. M. A. **108**:202 (Jan. 16) 1937.

254. Manville, I. A.: Use of Apple Powder in the Prevention and Cure of Summer Diarrheas, Arch. Pediat. **55**:76, 1938.

rationale for the treatment. Apparently he feels that the colloid hygroscopic action of pectin is capable of adsorbing large numbers of bacteria, but he also feels that uronic acid, which apples contain in amounts up to more than 1 per cent, is an important factor. He says that mucus is composed of a protein fraction and a carbohydrate fraction, the latter being glycuronic acid, which can be synthesized from the uronic acid contained in apples. Hence, the failure of mucous secretion associated with vitamin A deficiency may be in part overcome by the feeding of uronic acid. It might be assumed that the overproduction of mucus in acute diarrhea could be prevented in part by similar therapy.

Another form of treatment for diarrhea based on restoring the intestinal mucus is that suggested by Goth.[255] After the work of Felix, who demonstrated the presence of an enzyme, histaminase, in an extract of dried intestinal mucus ("torantil") Goth attempted the use of the extract in the treatment of intestinal "allergy." He concludes that relief should be afforded by either of the following mechanisms:

1. Prevention of the formation of histamine
   (*a*) Removal of allergens
   (*b*) Desensitization to allergens
2. Minimization of the histamine effect
   (*a*) Accustomization (histamine feeding)
   (*b*) Destruction (by extract of dried intestinal mucus)

He feels, of course, that the preparation of dried intestinal mucus acts by destruction of histamine in situ through its enzyme activity. The work is published with no statistical data and with no clinical evidence for the statement that the patients were in fact suffering from intestinal allergy. If the finding of histaminase by Felix is correct, then Goth's therapeutic attempts are rational and of great theoretic interest and should be repeated in a more thorough manner.

Reverting to the subject of Hirschsprung's disease, Reeves and Harrison [256] report on the effect of the administration of pancreatic extract. Craven, in 1934, introduced the treatment on the theory that extract of pancreatic tissue is a parasympathetic stimulant. She had demonstrated that it has an immediate effect on the intestines of the guinea pig. Reeves and Harrison used the Sharp & Dohme preparation of pancreatic tissue in acid alcohol. They gave doses up to 3 cc. daily and show the roentgenograms taken in 3 cases in which there was striking improvement. They say that they obtained striking improvement in 6 of 8 patients who received this treatment.

255. Goth, A.: Ueber die Behandlung der Kolitis mit Torantil, Deutsche med. Wchnschr. **64**:338, 1938.

256. Reeves, R. J., and Harrison, E. K.: The Treatment of Hypotonic Megacolon by Administration of Pancreatic Tissue Extract, Radiology **28**:731, 1937.

Book Reviews

Porphyrine und Porphyrinkrankheiten. By. A. Vannotti, M.D., of the University Clinic, Bern. Price, 27 marks. Pp. 286, with 64 illustrations. Berlin: Julius Springer, 1937.

This is an unusually interesting book and deals with a subject which is of considerable clinical interest. It is divided into ten chapters; the first seven are devoted to the porphyrins, their chemical composition, their importance in biology and their relation to pigment and iron metabolism in general. The eighth and ninth chapters deal with the clinical manifestations of porphyria and their treatment. The tenth chapter is concerned with methods and describes how porphyrin may be quantitatively measured in blood, urine and bile.

The monograph as a whole emphasizes the importance of differentiating between normal and abnormal porphyrin metabolism. The author designates the latter porphyria. He discusses the cutaneous, abdominal and nervous manifestations that may be induced by abnormal porphyrin metabolism. In the chapter on treatment he discusses what may be attempted in the light of current knowledge and leaves one with the feeling that much more is now understood about porphyria than was clear a few years ago. While therapeutic methods to combat this disorder are by no means wholly successful, it is possible at least to control porphyrin metabolism to a certain extent, to mobilize the deposit of porphyrin in the bones and to stimulate its excretion through the kidneys in several ways.

At the end of each chapter is a comprehensive bibliography. In glancing through the references one obtains the impression that comparatively little significant work on porphyrin metabolism has been accomplished in this country; the vast majority of the references are either to the German or the English literature. The book as a whole is well and interestingly written. It deserves recognition.

Dextrose Therapy in Everyday Practice. By E. Martin, Sc.D. Price, $3. Pp. 451, with 44 illustrations. New York: Paul B. Hoeber, Inc., 1937.

This book presents a survey of the clinical and experimental investigations which were reported between 1900 and 1936 concerning the role of dextrose in normal and abnormal physiologic conditions and its use as a therapeutic agent. The material is exceedingly well organized and is clearly and concisely presented in a practical and usable manner. After a short historical introduction the chemistry of dextrose is discussed, followed by an excellent chapter on its "physiologic action." The author then considers dextrose therapy in diseases of the various systems of the body (gastrointestinal and cardiovascular); in metabolic, deficiency, allergic and infectious diseases; in pregnancy, and in surgical conditions. A separate chapter is devoted to each group of disorders; the symptomatology and pathologic physiology are discussed and the rationale for and therapeutic value of the administration of dextrose are indicated. The final chapter deals with the modes of administration of dextrose. An extensive bibliography is appended to each chapter, amounting in all to over two thousand references. Although numerous statements in the book are controversial and at times dextrose therapy appears in the light of a universal panacea, the monograph is exceedingly valuable, summarizing in a practical way the present status of knowledge of the importance of dextrose in bodily economy and in therapy.

Neurology. By Roy R. Grinker, M.D. Second edition. Price, $8.50. Pp. 999, with 406 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1937.

As a textbook for students this volume should rank high, as the subject matter is arranged to meet the requirements of the students in an understandable way.

In a textbook on neurology, like one on psychiatry, it is a difficult problem to keep up with the times, as no branches of medicine are receiving more attention and more contributions from scientific minds than are neurology and psychiatry. This is true especially in the line of therapy. On perusing the different chapters of this book and noting the many changes necessary since the issue of the first edition, one must conclude that as an up-to-date textbook it can be recommended. The author has reviewed the recent literature rather thoroughly on the subjects which have attracted those who have given the most time to research. The chapter devoted to the extrapyramidal motor system, as evidenced by the number of references at the end of the chapter, is a good example of the attention given that subject within the past few years, which has shown the interpretation of the pathologic picture of the disease through clinical demonstration. The illustrations are well arranged and instructive.

Neuere Ergebnisse auf dem Gebiete der Krebskrankheiten. By Prof. Dr. C. Adam and Prof. Dr. H. Auler. Price, 12 marks. Pp. 366, with 66 illustrations. Leipzig: S. Hirzel, 1937.

Forty-seven prominent German authors have collaborated in the presentation of this volume on the subject of carcinoma. The purpose of the compilation is an exposition of the more recent concepts and the more advanced studies on cancer. Each of the various phases of carcinoma is considered in a separate article by an author interested in that particular aspect of the problem.

Professor Dietrich, in discussing the relation of trauma to the development of carcinoma, expresses the view that there has been a tendency to stress this unduly. He states that there are several factors that must work together for the production of tumor, namely, (1) disposition; (2) tumor anlage (embryonal) and (3) cell mutation. According to Professor Schultz, the cachexia associated with carcinoma is the result of autointoxication, due either to break-down products or a secretion of the carcinoma cells. The bluish stippling of the red blood cells observed in some cases of cancer is accordingly a manifestation of toxic degeneration.

Professor Frik states that, in contrast to most American surgeons, Germans prefer postoperative rather than preoperative roentgen therapy in the management of carcinoma of the breast. Of interest in this regard is the statement by Professor Buetzur that there is no danger of metastasis as a result of biopsy. Professor Braun sounds a disconsolate note in his excellent summary of the recorded observations on carcinoma of the liver and pancreas. The interesting analysis of 1,301 cases of rectal carcinoma by Professor Bench is especially noteworthy. Whereas the obtaining of a five year cure in 10 per cent of the cases may appear encouraging, his statement that 75 per cent of all physicians coming to the surgeon have inoperable lesions is most discouraging.

Other articles consider carcinoma of the skin, lungs, prostate and other organs and regions. These give, in general, good summaries and reviews, with expressions of the authors' impressions and a consideration of German opinions.

Eksperimentelle studier over occlusionsicterus. By Orla Vadsten. Pp. 288, with 19 figures and an English summary. Copenhagen: Nyt Nordisk Forlag, Arnold Busck, 1936.

This interesting dissertation is based on rat experiments done at the Institute for Hygiene of the University of Copenhagen and contributes substantially to the knowledge of the abnormal physiology of the obstructive jaundice produced by cutting the ductus choledochus between ligatures. The author considers the question as to which is more important in this condition, (1) the disturbance of digestion and absorption that results from the exclusion of bile from the intestine or (2) the disturbance directly produced in the rest of the body by the bile pigments and bile salts circulating in the body fluids. His experiments confirm the suspicion, based on a thorough review of previous work, that the consequences of obstructive jaundice are primarily digestive and absorptive.

When kept on a standard diet, rats with obstructive jaundice showed no signs of avitaminosis D, and the only sign of avitaminosis A was chronic colpokeratosis. Such rats were more resistant than normal rats to toxic doses of vitamin D given by mouth, but not to vitamin D given subcutaneously. They did not gain in weight if vitamin A was added to the food, but they did if vitamin A was given subcutaneously. When rats with obstructive jaundice were kept on a special diet shown to be adequate for normal rats, severe xerophthalmia developed. Of the 337 rats in which obstructive jaundice was produced, 20.5 per cent had "cholemic" hemorrhages; certain data indicate that the bleeding was associated with reduced absorption of vitamin D. Other results and control procedures which cannot be summarized here are described in the detailed English summary. The bibliography shows a thorough knowledge of recent American work.

Pneumatiseringen og de bestaaendelsesagtige forandringer i processus mastoideus ved mellemøresuppuration; en kliniksk-roentgenologisk studie. By Kurte Bröste, M.D.

This roentgenologic study of pneumatization of the mastoid and of changes observed associated with suppuration of the middle ear was presented by Dr. Bröste as a thesis for the degree of Doctor of Medicine at the University of Copenhagen. One hundred and thirty-four patients were examined along with their clinical histories. It was hoped that such an associated examination would correlate diseases of the middle ear with the changes in the mastoid.

His basic hypothesis was that the degree of mastoid pneumatization is dependent on the vitality of the epithelium of the tympanic cavity and, therefore, that the anatomic development of the mastoid is to be considered as a function of the character of the mucous membrane of the middle ear and that diseases in the middle ear and in the mastoid might therefore be expected to show a correlation. He accepts Wittmaack's classification of three chief variants in the mucoperiosteum of the ear—mesoplastic or normal, hyperplastic and fibrinous. His studies, however, did not support the hypothesis that a special variety of mastoid occurs with either the fibrinous or the hyperplastic type. Suppuration of the middle ear with a mesoplastic mucosa may be expected to run a favorable course. But he was not able to determine definitely a special part played by these variants in pneumatization or on the outcome of mastoiditis.

He sought for a definite picture associated with sinus thrombosis or perisinus abscess, but such could not be determined. Distortion of the contour of the lateral sinus he found to be an untrustworthy guide, since the normal sinus does not always show sharply defined walls.

Though he expresses regret that he was unable to establish any relation between the type of pneumatization and any definite tendency toward complications of the various types, his study is of value because of the variety and significance of the individual cases.

Experimentelle Untersuchungen über das Blut und die blutbildenden Organe besonders das lymphatische Gewebe des Kaninchens bei wiederholten Aderlässen. By Helge Sjövall. Pp. 308, with tables and charts. Lund: Häikan Ohlssons Buchdruckerei, 1936.

This volume represents an original contribution to the hematologic literature and was "primarily intended to clarify the part played by the lymphatic tissue, and especially the secondary nodules, in lymphocyte production." Rabbits made anemic by repeated bleeding were used as test animals. Many data were obtained, not only on hematologic factors but regarding lymphatic structures as well. Results speak against the secondary nodules as main centers of formation of lymphocytes and for the hypothesis of lymphocytic circulation, with movement from the lymphatic tissue through the blood to the body tissues and back again.

While the book seems unduly long for a report of the studies carried out, one must commend the completeness of the data given. Profuse illustration with charts and tables covers all details of the investigation, including the values of

statistical analysis. The thoroughness and accuracy of the observations are immediately evident. The volume, however, will interest a small group only. The practitioner will find in it little or nothing to attract his attention. It is of value primarily to the research pathologist and hematologist.

Der Myokardinfarkt: Erkennung, Behandlung und Verhütung. By Prof. Max Hochrein, M.D., Chief of Medicine in the University Clinic, Leipzig. Price, 12.50 marks. Pp. 196, with 52 illustrations. Dresden: Theodor Steinkopff, 1937.

This book, representing the first of a series on the circulation, considers myocardial infarction from the standpoint of diagnosis, management and prevention. One is introduced to the important aspects of the anatomy of the coronary system first and then to the problems of physiology and pathologic physiology. In this way the hemodynamics of the coronary system are made a basis for an understanding of the superstructure, the clinical aspects of coronary occlusion. Particularly emphasized in this connection are the analysis of the symptoms, the diagnosis, including electrocardiographic localization, the differential diagnosis and the treatment.

The work represents an excellent short review of those aspects of coronary disease of greatest interest to the practicing physician. Controversial and theoretic considerations are reduced to a minimum, leaving for the reader a clear but brief exposition of the necessary facts. Another important feature of the book is the breadth of the literature included in its preparation. American works are well represented and are incorporated with European views in the problems of pathogenesis and diagnosis.

An extensive bibliography is appended.

Die inneren Erkrankungen im Alter. By Albert Müller-Deham, M.D. Price, 24 marks. Pp. 408. Berlin: Julius Springer, 1937.

Without doubt the medical problems of old age will become increasingly important as the average span of life is prolonged. Moreover, old persons prefer to live comfortably and to remain active as long as they can; hence how best to manage effectually the latter years of life is an important medical problem.

This volume is a textbook on disease as it appears in elderly persons. The author points out that elderly persons react differently to illnesses than do younger ones; cancer, diabetes, the anemias, pneumonia, for example, all are likely to develop in older persons, to respond differently to treatment than in younger persons and to require different management. The cost of surgical treatment is greater in the old person than in the young, not only because convalescence after an operation is longer but also because there is less time left for postoperative accomplishment. Hence, when and how to operate on old persons requires a special kind of surgical judgment.

All such matters and many more are discussed in this book. On the whole, it presents an interesting point of view on an interesting phase of medicine. While a textbook of this character is not likely to be widely read, it is a stimulating reference work. It is worth having on the shelves of any medical library.

Normale und pathologische Physiologie der Bewegungsvorgänge im gesamten Verdauungskanal. Vol. 2. By Prof. Dr. Med. Werner Catel. Price, 15 marks. Pp. 298, with 123 illustrations. Leipzig: Georg Thieme, 1937.

This is the second volume of Professor Catel's thorough work on the motility of the digestive tract. The present instalment is in two parts; the first takes up clinical pathology under such heads as the pathology of swallowing, esophageal spasms and dilatations, pyloric spasms, dilatation of the stomach and so on down the digestive tract. The last section is on pharmacology and deals with the influence of the various common drugs in this domain. The book is handsomely printed, with many excellent illustrations and diagrams as well as an extensive bibliography.